

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

S. Asciglu,¹ J. H. Rex,² B. de Pauw,¹ J. E. Bennett,² J. Bille,¹ F. Crokaert,¹ D. W. Denning,¹ J. P. Donnelly,¹ J. E. Edwards,² Z. Erjavec,¹ D. Fiere,¹ O. Lortholary,¹ J. Maertens,¹ J. F. Meis,¹ T. F. Patterson,² J. Ritter,¹ D. Selleslag,¹ P. M. Shah,¹ D. A. Stevens,² and T. J. Walsh,² on behalf of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases

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

During the past several decades, there has been a steady increase in the frequency of opportunistic invasive fungal infections (IFIs) in immunocompromised patients. However, there is substantial controversy concerning optimal diagnostic criteria for these IFIs. Therefore, members 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 formed a consensus committee to develop standard definitions for IFIs for clinical research. On the basis of a review of literature and an international consensus, a set of research-oriented definitions for the IFIs most often seen and studied in immunocompromised patients with cancer is proposed. Three levels of probability are proposed: “proven,” “probable,” and “possible.” The definitions are intended for use in the context of clinical and/or epidemiological research, not for clinical decision making.

Opportunistic invasive fungal infections (IFIs) are a major cause of morbidity and mortality in immunocompromised patients. However, there still remains much uncertainty and controversy regarding the best methods for establishing the diagnosis of most IFIs. Practicing physicians approach this uncertainty by treating suspected cases empirically, whereas those who

review cases for research purposes tend to accept only cases in which the diagnosis is certain. This disparity of approaches is particularly apparent in the conduct of clinical trials designed to show that a new drug exhibits sufficient efficacy.

These difficulties are not unique to the study of IFIs, and wide practice variations are known to exist in all areas of medicine [1, 2]. The uncertainty in disease definition is thought to be a key contributor to these variations [1]. Strategies to minimize such uncertainties have resulted in movements such as evidence-based medicine [3] and practice guidelines [4]. In studies in which there is no assurance that homogeneous populations are being evaluated, the selection of study subjects may be biased and, therefore, their findings cannot be used to make generalizations about cause, epidemiology, prognosis, treatment, or prevention [5]. Typically, a set of characteristic abnormalities is used for diagnosis of dis-

Received 3 November 2000; revised 14 May 2001; electronically published 26 November 2001.

Financial support: Unrestricted educational grant from Pfizer (to S.A.); European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (to S.A.); Aronex, Janssen Research Foundation, Liposome Company, NeXstar-Gilead, and Pfizer.

Reprints or correspondence: Dr. Thomas J. Walsh, National Cancer Institute, 9000 Rockville Pike, Bldg. 10, Rm. 13N240, Bethesda, MD 20892 (walsht@mail.nih.gov).

Clinical Infectious Diseases 2002;34:7–14

© 2002 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2002/3401-0002\$03.00

eases that do not have pathognomonic signs. Such classification and diagnostic criteria have proven to be extremely useful in areas that involve rheumatic diseases, endocarditis, and psychiatric diseases [6–8]. Also, subdivision by certainty of diagnosis is useful in many situations in which definite criteria cannot be applied to all cases [9]. A series of estimates of probability (e.g., definite, proven, suspected, presumptive, and probable) is also a part of all of these systems, which is also evident from the literature on IFIs [10]. Unfortunately, even these terms may take a range of meanings, and there is thus wide variation in their interpretation [11]. The resulting array of descriptive phrases makes it difficult to pool data from multiple centers and thus hinders drug development, impedes the pace of clinical research, and perpetuates confusion in the literature. Although there are reference standards for diagnosing IFIs, these usually involve use of invasive procedures to obtain tissue specimens for culture and histological examination. Unfortunately, these procedures are not always feasible. Therefore, clinicians caring for such patients may rely on a combination of less-specific clinical, laboratory, and radiological data. Indeed, situations that present significant diagnostic uncertainty are the norm for most IFIs, and diagnostic criteria with perfect sensitivity and specificity do not exist for any IFI or, indeed, for many other diseases [12–16].

In an effort to standardize the definitions of IFIs for clinical research, the Invasive Fungal Infections Cooperative Group (IFICG) of the European Organization for Research and Treatment of Cancer (EORTC) convened a committee of EORTC/IFICG members with the goal of defining and classifying the IFIs that are commonly seen and studied in immunocompromised patients with cancer. At a later stage, members of the Mycoses Study Group (MSG) of the National Institute of Allergy and Infectious Diseases (NIAID) subsequently joined this consensus effort. This document is the final result of the combined efforts of this consensus committee, on the basis of several rounds of discussion that culminated in the approval of the document.

The committee sought to develop definitions for clinical researchers that were based on published information, deemed clinically applicable by experienced researchers, and practical within the context of the types of objectively verifiable data generated in daily clinical practice. Of importance, these guidelines should not be taken as strict rules for making or excluding the diagnosis of an IFI in clinical settings.

METHODS

Defining the problem. A systematic review of the literature for an explicit identification of major problems related to heterogeneity of immunocompromised patients with cancer who have IFIs was undertaken and is described elsewhere [10]. *Pneu-*

mocystis infections were not considered. In brief, the abstracts of 7086 articles published from 1985 through 1997 were screened. Of these, 173 articles were finally selected because they were reports exclusively regarding clinical research on immunocompromised patients with cancer or recipients of hematopoietic stem cell transplants who also had deep-tissue fungal infections. The minimum diagnostic criteria used to include patients in the study were extracted from definitions devised by the investigators. Likewise, the criteria used to express different degrees of diagnostic probability were summarized, as were the terms most often used to express these levels of uncertainty.

Construction and function of the consensus committee.

The IFICG, 1 of the 16 cooperative groups of the EORTC, created a task force in March 1997 under the chairmanship of Dr. Ben E. de Pauw. This initial committee consisted of 12 members of the IFICG from 8 different countries. Members of NIAID MSG were asked to join this committee in 1998.

The committee began with the information from the literature review, and each committee member was asked to provide comments on the terms and the construction they preferred. These comments led to revisions of the draft document in a cycle that was repeated many times until a final consensus was reached. During this process, the consensus committee also met face-to-face twice to discuss the proposal. In addition, the proposal was discussed in 3 group meetings of EORTC/IFICG, where it was open to all members of IFICG for discussion.

RESULTS

The definitions. We propose definitions for a new classification based on the level of certainty for the diagnosis of IFIs (tables 1 and 2). This proposal includes both diagnostic criteria for proven IFIs and also classification criteria for probable and possible diseases that are intended to promote a more uniform description of the patients when various research endeavors are reported.

The committee chose the terms “proven,” “probable,” and “possible” to express disease certainty. Although other terms could be used, our literature review showed a clear trend among investigators favoring the use of these terms. These verbal expressions of subjective probability correspond to a reasonably accurate numerical estimate [12, 14]. Three elements form the basis of the proposed definitions: host factors, clinical manifestations, and mycological results.

Host factors. We restricted the scope of the definitions to patients with cancer, whether treated or not, and to recipients of hematopoietic stem cell transplants who were suspected of having an IFI. However, because these patients do not present a single uniform entity, additional host factors

Table 1. Definitions of invasive fungal infections in patients with cancer and recipients of hematopoietic stem cell transplants.

Category, type of infection	Description
Proven invasive fungal infections	
Deep tissue infections	
Molds ^a	Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging); or positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes
Yeasts ^a	Histopathologic or cytopathologic examination showing yeast cells (<i>Candida</i> species may also show pseudohyphae or true hyphae) from specimens of needle aspiration or biopsy excluding mucous membranes; or positive culture result on sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses, and mucous membranes; or microscopy (India ink, mucicarmine stain) or antigen positivity ^b for <i>Cryptococcus</i> species in CSF
Fungemia	
Molds ^a	Blood culture that yields fungi, excluding <i>Aspergillus</i> species and <i>Penicillium</i> species other than <i>Penicillium marneffei</i> , accompanied by temporally related clinical signs and symptoms compatible with relevant organism
Yeasts ^a	Blood culture that yields <i>Candida</i> species and other yeasts in patients with temporally related clinical signs and symptoms compatible with relevant organism
Endemic fungal infections ^c	
Systemic or confined to lungs	Must be proven by culture from site affected, in host with symptoms attributed to fungal infection; if culture results are negative or unattainable, histopathologic or direct microscopic demonstration of appropriate morphological forms is considered adequate for dimorphic fungi (<i>Blastomyces</i> , <i>Coccidioides</i> and <i>Paracoccidioides</i> species) having truly distinctive appearance; <i>Histoplasma capsulatum</i> variant <i>capsulatum</i> may resemble <i>Candida glabrata</i>
Disseminated	May be established by positive blood culture result or positive result for urine or serum antigen by means of RIA [17]
Probable invasive fungal infections	At least 1 host factor criterion (see table 2); and 1 microbiological criterion; and 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection
Possible ^d invasive fungal infections	At least 1 host factor criterion; and 1 microbiological or 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection

^a Append identification at genus or species level from culture, if available.

^b False-positive cryptococcal antigen reactions due to infection with *Trichosporon beigelii* [1], infection with *Stomatococcus mucilaginosus* [2], circulating rheumatoid factor [3], and concomitant malignancy [4] may occur and should be eliminated if positive antigen test is only positive result in this category.

^c Histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis.

^d This category is not recommended for use in clinical trials of antifungal agents but might be considered for studies of empirical treatment, epidemiological studies, and studies of health economics.

need to be considered when confronted with IFIs that cannot be proven. Those additional factors (table 2) reflect the literature and the opinions of the consensus committee. The criteria for proven IFIs are likely valid for all host groups, not just patients with cancer and recipients of hematopoietic stem cell transplants.

Mycological evidence. Mycological evidence begins with the specimen. Thus, specimens obtained from normally sterile but clinically abnormal sites were rated to be more reliable than were those obtained from adjacent normal sites or sites normally colonized with resident commensal flora. These specimens were considered necessary for proving IFIs. Hence, the mycological evidence acquired by means of either direct examination or culture of specimens from sites that may be col-

onized (e.g., sputum, bronchoalveolar lavage fluid, or sinus aspirate) were thought only to support the diagnosis, not prove it. Similarly, with the sole exception of *Cryptococcus neoformans*, indirect tests to detect antigen were considered to be suggestive but not conclusive. Thus, the nature and quality of the specimen and the use of direct and indirect mycological techniques were incorporated into each of the criteria.

Clinical features. An attempt was made to distinguish between evidence of abnormality of an organ or organ system that was consistent with an IFI from evidence that could be associated with another infective process. For example, evidence of abnormal appearance by radiological or other imaging was given a much higher rating than were other, less specific signs, such as pleural rub. Symptoms and some other clinical features

Table 2. Host factor, microbiological, and clinical criteria for invasive fungal infections in patients with cancer and recipients of hematopoietic stem cell transplants.

Type of criteria	Criteria
Host factors	<p>Neutropenia (<500 neutrophils/mm³ for >10 days)</p> <p>Persistent fever for >96 h refractory to appropriate broad-spectrum antibacterial treatment in high-risk patients</p> <p>Body temperature either >38°C or <36°C and any of the following predisposing conditions: prolonged neutropenia (>10 days) in previous 60 days, recent or current use of significant immunosuppressive agents in previous 30 days, proven or probable invasive fungal infection during previous episode of neutropenia, or coexistence of symptomatic AIDS</p> <p>Signs and symptoms indicating graft-versus-host disease, particularly severe (grade ≥2) or chronic extensive disease</p> <p>Prolonged (>3 weeks) use of corticosteroids in previous 60 days</p>
Microbiological	<p>Positive result of culture for mold (including <i>Aspergillus</i>, <i>Fusarium</i>, or <i>Scedosporium</i> species or Zygomycetes) or <i>Cryptococcus neoformans</i> or an endemic fungal pathogen^a from sputum or bronchoalveolar lavage fluid samples</p> <p>Positive result of culture or findings of cytologic/direct microscopic evaluation for mold from sinus aspirate specimen</p> <p>Positive findings of cytologic/direct microscopic evaluation for mold or <i>Cryptococcus</i> species from sputum or bronchoalveolar lavage fluid samples</p> <p>Positive result for <i>Aspergillus</i> antigen in specimens of bronchoalveolar lavage fluid, CSF, or ≥2 blood samples</p> <p>Positive result for cryptococcal antigen in blood sample^b</p> <p>Positive findings of cytologic or direct microscopic examination for fungal elements in sterile body fluid samples (e.g., <i>Cryptococcus</i> species in CSF)</p> <p>Positive result for <i>Histoplasma capsulatum</i> antigen in blood, urine, or CSF specimens [17]</p> <p>Two positive results of culture of urine samples for yeasts in absence of urinary catheter</p> <p><i>Candida</i> casts in urine in absence of urinary catheter</p> <p>Positive result of blood culture for <i>Candida</i> species</p>
Clinical	<p>Must be related to site of microbiological criteria and temporally related to current episode</p>
Lower respiratory tract infection	
Major	Any of the following new infiltrates on CT imaging: halo sign, air-crescent sign, or cavity within area of consolidation ^c
Minor	Symptoms of lower respiratory tract infection (cough, chest pain, hemoptysis, dyspnea); physical finding of pleural rub; any new infiltrate not fulfilling major criterion; pleural effusion
Sinonasal infection	
Major	Suggestive radiological evidence of invasive infection in sinuses (i.e., erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction)
Minor	Upper respiratory symptoms (e.g., nasal discharge, stuffiness); nose ulceration or eschar of nasal mucosa or epistaxis; periorbital swelling; maxillary tenderness; black necrotic lesions or perforation of hard palate
CNS infection	
Major	Radiological evidence suggesting CNS infection (e.g., mastoiditis or other parameningeal foci, extradural empyema, intraparenchymal brain or spinal cord mass lesion)
Minor	Focal neurological symptoms and signs (including focal seizures, hemiparesis, and cranial nerve palsies); mental changes; meningeal irritation findings; abnormalities in CSF biochemistry and cell count (provided that CSF is negative for other pathogens by culture or microscopy and negative for malignant cells)
Disseminated fungal infection	Papular or nodular skin lesions without any other explanation; intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis
Chronic disseminated candidiasis	Small, peripheral, targetlike abscesses (bull's-eye lesions) in liver and/or spleen demonstrated by CT, MRI, or ultrasound, as well as elevated serum alkaline phosphatase level; supporting microbiological criteria are not required for probable category
Candidemia	Clinical criteria are not required for probable candidemia; there is no definition for possible candidemia

^a *H. capsulatum* variant *capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, or *Paracoccidioides brasiliensis*.

^b See table 1 footnote *b* for causes of false-positive reactions that must be considered and eliminated from consideration.

^c In absence of infection by organisms that may lead to similar radiological findings including cavitation, such as *Mycobacterium*, *Legionella*, and *Nocardia* species.

were also regarded as less specific and only supportive. Thus, 2 levels of evidence (major and minor) were incorporated into the concept of clinical features of IFIs.

DISCUSSION

The consensus for many of the definitions was determined after extensive debate. In many cases, that debate is instructive and elements of it are reviewed here.

Proven category of infections. The “proven” category consists of criteria that allow IFIs to be diagnosed with certainty and that differentiates between deep-tissue infections and fungemia. There was general agreement among committee members that the highest level of certainty in diagnosing an invasive fungal infectious disease is attained by establishing the presence of fungi in tissue by biopsy or a needle aspirate. However, the committee also agreed that demonstration of infection either by culture or histological examination was sufficient to be able to distinguish molds from yeasts and that both, although desirable, were not strictly necessary.

A branching septate mold in tissue is most commonly *Aspergillus* species. However, other organisms, including hyaline and dematiaceous molds, may be morphologically indistinguishable from *Aspergillus* species. A Fontana-Masson stain may help to distinguish hyaline from dematiaceous organisms. By comparison, the histological appearance of the ribbon-like broad coenocytic (sparsely septated) hyphal structures of Zygomycetes is usually readily distinguishable from *Aspergillus* species and other septated molds. The histological appearance of the endemic dimorphic fungi—*Histoplasma capsulatum*, as small intracellular budding yeasts; *Coccidioides immitis*, 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 as to permit a definitive diagnosis as proven fungal infection caused by 1 of these pathogens. Whenever culture is possible, a specific diagnosis to the species level should be provided.

We propose that either typical microscopic findings or the detection of antigen in CSF be accepted as diagnostic for cryptococcosis in an immunocompromised host in the appropriate clinical setting [18]. It is, however, important to be aware of the rare but definite causes of a false-positive cryptococcal antigen result, including infection caused by *Trichosporon* species [19], infection with *Stomatococcus mucilaginosus* [20], presence of circulating rheumatoid factor [21], and concomitant malignancy [22].

For the purposes of these definitions, the committee preferred the term “fungemia” to “bloodstream fungal infections,” because this avoids the impression that isolating a fungus from culture of blood signifies an infection that is confined to the

bloodstream. For *Fusarium* species and *Penicillium marneffei*, fungemia, more likely than not, represents deep-tissue infection. Culture of *Aspergillus* species and other *Penicillium* species from the blood may represent serious disease but is more likely to represent specimen contamination; therefore, it is not taken as proof of diseases for purposes of clinical research.

Probable and possible categories of infection. Patients in these categories present enough information suggesting an IFI to warrant some form of empirical antifungal therapy. These patients are frequently characterized by being febrile, despite receipt of broad-spectrum antibiotics, and they may have a potential focus of infection. A definitive tissue diagnosis for radiologically demonstrable lesions, if present, is not considered feasible. Many independent reviewers would dismiss these cases for lack of convincing evidence. The problem of uncertainty cannot be understated or disregarded as if it does not exist, because both clinicians and researchers are regularly confronted with it. Rather, we sought to incorporate uncertainty into our quest for diagnosis and translate it into probabilities as accurately as possible [15, 16]. For a case of IFI to be considered “probable,” each of the 3 elements of host factor, clinical features, and mycological evidence has to be present [23]. By contrast, a patient who has at least 1 criterion from the host factors category but who does not have clinical features or mycological evidence has a case that can be classified only as “possible.” Because this is the least specific category, but one often used in clinical practice to treat patients empirically, we do not recommend its use in clinical trials of antifungal agents. Rather, it might be considered in studies of empirical treatment, epidemiological studies, and studies of health economics.

Aspergillosis. Because culture has such a poor sensitivity in the diagnosis of invasive aspergillosis, reliance on culture alone results in substantial underdiagnosis. On the other hand, cultures that yield *Aspergillus* species do not always reflect invasive disease, because colonization can occur in immunocompromised patients, and false-positive results that result from environmental contamination are occasionally a problem. Thus, the committee strongly supported the concept of a proven mold infection on the basis of the findings of histopathology or microscopy without necessarily requiring culture confirmation. The committee also proposed use of *Aspergillus* antigen testing as a finding that would support a probable diagnosis. The detection of *Aspergillus* antigenemia has been shown in experimental assays to correlate with clinical diagnosis and response to antifungal therapy [24, 25]. However, the clinical utility of these assays has been limited, in part because of their lack of widespread availability. Recently, a sandwich ELISA technique that uses a monoclonal antibody to galactomannan has been developed [26]. This assay (licensed by Sanofi Diagnostics Pasteur to Bio-Rad Laboratories) has been used most extensively in western Europe. Recent prospective studies of

hematology patients have demonstrated a sensitivity and specificity of >90% with this method [27]. Of note, there have been false-positive reactions, with recommendations from the manufacturer to consider the test a true-positive result only when >1 sample is positive. The use of PCR to detect invasive fungal pathogens, including *Aspergillus* species, has been reported, but false-positive results can occur, and a standardized commercial method is not available [28]. Thus, the committee decided that at the present time, the routine use of PCR in the diagnosis of invasive aspergillosis cannot be recommended.

Candidemia. Although other presentations are possible and are recognized by the definitions, candidemia is taken as a key sign of disseminated candidiasis. However, significant controversy surrounds the interpretation of positive blood culture results for candidemia [29]. In reviewing these controversies, the committee recognized that not all groups of patients with candidemia have the same risk of clinically significant widespread dissemination. The principal classification factor is the presence or absence of neutropenia. Patients with neutropenia have a much higher rate of provable visceral dissemination and a much higher mortality rate [30]. Although similar diagnostic criteria are applied to the 2 groups, patients with and without neutropenia cannot rationally be aggregated for purposes of data analysis. Also of note, candidemia, rather than being too nonspecific, is instead a marker (although insensitive) of deeply invasive candidiasis—that is, culture of blood samples often yields negative results in the presence of deep visceral candidiasis [31].

The second major subdivision of patients with candidemia revolves around the presence or absence of a central venous catheter. Broad dismissal of positive results of culture of blood from patients who have a central venous catheter in place is inappropriate. However, it is certainly possible that specimens drawn through a catheter would become contaminated during the collection process. The committee considered addressing this with requirements for specific numbers of blood cultures but thought that this was impractical. Although increasing numbers of positive blood culture results have been correlated with the likelihood of significant invasion [32], final blood culture data may not exist at the time a patient is considered for eligibility in a trial. In a related problem, the relevance of the site from which the culture-positive blood specimen was obtained was extensively discussed. Cultures obtained via peripheral venipuncture or through a newly inserted catheter would seem preferable on the general grounds that the catheters, rather than the patient, may be the cause of a culture-positive specimen. However, it is also clear that catheters may represent a major intravascular nidus of infection and that sampling via the catheter may provide early indication of a problem that has yet to reach a stage at which it can be detected in a more dilute specimen obtained from a remote site. In

addition, records on the precise site at which a blood specimen was obtained are not consistently available or accurate. A comprehensive review of 155 episodes of catheter-related candidemia in patients with cancer found that, regardless of whether blood cultures were obtained from a central catheter or peripheral site, the frequency of autopsy-proven candidiasis was the same [32]. Thus, the committee elected to establish no specific requirements for the site from which the specimen was obtained. To resolve all of these challenges, heavy reliance was placed on the requirement for concomitant signs of infection.

Patients with candidemia who have temporally related signs of infection are always considered to have a significant, proven infection. Given that the signs and symptoms are incorporated into the definition of proven candidemia, the category of probable candidemia relies on host factors and microbiological factors. Patients with neutropenia, patients with graft-versus-host disease, or patients receiving corticosteroids who have candidemia without signs of infection are considered to have probable disease. But, for example, patients who have neutropenia and candidemia, who do not have signs of infection, and who do not also meet ≥ 1 of the other “host factors” criteria are considered to have a disease process that cannot reasonably be studied within the guidelines of this document. Although such patients should probably still receive some form of therapy [33], their relevance to a clinical trial is uncertain. The committee decided not to incorporate and define a “possible” category for candidemia. The definition for chronic disseminated candidiasis (hepatosplenic candidiasis) likewise required a modification because of the infrequency of microbiological support for this condition. For this diagnosis, the committee decided not to define a “possible” category, and for chronic disseminated candidiasis only, a microbiological criterion is not required for a “probable” diagnosis in a suitable host.

Other forms of invasive candidiasis. Other forms of invasive candidiasis are handled in 2 ways. First, any situation in which a biopsy of a normally sterile site shows *Candida* species by culture or histopathologic examination will qualify as proven candidiasis. Because of the many possible permutations (e.g., candidemia, candidemia with hepatosplenic involvement, hepatosplenic involvement without candidemia), the definitions do not specifically contain a list of possible relevant categories. Rather, these are all grouped under the general title of “proven invasive candidiasis.”

More challenging are the scenarios in which *Candida* species are isolated from such specimens as urine, sputum, or wound drainage. A very conservative approach was taken here. Although a rational physician might well choose to give antifungal therapy to a patient with fever and *Candida* species in the urine (or sputum, or wound drainage), this scenario is simply too ill-defined for study in a clinical trial.

Comparison with earlier NIAID MSG definitions. The

proposed definitions in this manuscript differ from the earlier NIAID MSG definitions by focusing on the specific issues of oncology and hematopoietic stem cell transplantation. They recognize that the interplay of host factors and clinical manifestations may enhance the diagnostic probability of an IFI. The committee recognized that not all patients with neutropenia have the same risk for development of IFIs [34]. For example, recovering *Aspergillus* species from the respiratory secretions of a patient with profound neutropenia who has acute leukemia or a patient receiving high dosages of corticosteroids carries much more significance for the development of invasive aspergillosis than it does when *Aspergillus* species are recovered from a patient with lung cancer and transient immunosuppression [35]. The new system now also incorporates the use of galactomannan antigen in defining invasive aspergillosis.

Limitations of these definitions for clinical practice. These definitions should not be used to guide clinical practice. There are frequent clinical situations in the “possible” category in which therapy is warranted on empirical grounds. The objective of this project was to develop definitions that would identify reasonably homogeneous groups of patients for clinical research, as well as to foster international collaboration, design of clinical trials, and interpretation of new therapeutic interventions for management of IFIs in patients receiving cancer chemotherapy and those undergoing hematopoietic stem cell transplantation.

Acknowledgments

We acknowledge the contributions of P. Ljungman, M. Nucci, J. E. Patterson, G. Petrikos, M. A. Pfaller, M. G. Rinaldi, and C. Viscoli, who took part in the consensus committee meetings or sent us comments.

References

1. Eddy DM. Probabilistic reasoning in clinical medicine: problems and opportunities. In: Kahneman D, Slovic P, Tversky A, eds. *Judgement under uncertainty: heuristics and biases*. New York: Cambridge University Press, 1982:249–67.
2. Chassin MR, Koseoff J, Park RE, et al. Does inappropriate use explain geographic variations in the use of health care services? A study of three procedures. *JAMA* 1987;258:2533–7.
3. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312:71–2.
4. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Potential benefits, limitations, and harms of clinical guidelines. *BMJ* 1999;318:527–30.
5. Hyams KC. Developing case definitions for symptom-based conditions: the problem of specificity. *Epidemiol Rev* 1998;20:148–56.
6. International Study Group for Behçet's Disease. Evaluation of diagnostic ('classification') criteria in Behçet's disease—towards internationally agreed criteria. *Br J Rheumatol* 1992;31:299–328.
7. Hunder GG, Arend WP, Bloch DA, et al. The American College of

- Rheumatology 1990 criteria for the classification of vasculitis. *Arthritis Rheum* 1990;33:1065–7.
8. Bayer AS, Ward JI, Ginzton LE, Shapiro SM. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. *Am J Med* 1994;96:211–9.
9. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Prospective cohort studies: planning and execution. In: *Methods in observational epidemiology*, 2nd ed. New York: Oxford University Press, 1996:87–112.
10. Ascioğlu S, de Pauw BE, Donnelly JP, Collette L. Reliability of clinical research on invasive fungal infections: a systematic review of the literature. *Med Mycol* 2001;39:35–40.
11. Wallsten TS, Budescu DV, Rapoport A, Zwick R, Forsyth B. Measuring the vague meanings of probability terms. *J Exp Psychol Gen* 1986;115:348–65.
12. White E. The effect of misclassification of disease status in follow-up studies: implications for selecting disease classification criteria. *Am J Epidemiol* 1986;124:816–25.
13. Hunder GG. The use and misuse of classification and diagnostic criteria for complex diseases. *Ann Intern Med* 1998;129:417–8.
14. Bryant G, Norman GR. Expressions of probability: words and numbers [letter]. *N Engl J Med* 1980;302:411.
15. Kassirer JP. Our stubborn quest for diagnostic certainty. *N Engl J Med* 1989;320:1489–91.
16. Moskowitz AJ, Kuipers BJ, Kassirer JP. Dealing with uncertainty, risks, and tradeoffs in clinical decisions: a cognitive science approach. *Ann Intern Med* 1988;108:435–49.
17. Durkin MM, Connolly PA, Wheat LJ. Comparison of radioimmunoassay and enzyme-linked immunoassay methods for detection of *Histoplasma capsulatum* var. *capsulatum* antigen. *J Clin Microbiol* 1997;35:2252–5.
18. Walsh TJ, Chanock SJ. Diagnosis of invasive fungal infections: advances in nonculture systems. *Curr Clin Top Infect Dis* 1998;18:101–53.
19. Walsh TJ, Melcher GP, Lee JW, Pizzo PA. Infections due to *Trichosporon* species: new concepts in mycology, pathogenesis, diagnosis, and treatment. *Curr Top Med Mycol* 1993;5:79–113.
20. Chanock SJ, Toltzis P, Wilson C. Cross-reactivity between *Stomatococcus mucilaginosus* and latex agglutination for cryptococcal antigen [letter]. *Lancet* 1993;342:1119–20.
21. Engler HD, Shea YR. Effect of potential interference factors on performance of enzyme immunoassay and latex agglutination assay for cryptococcal antigen. *J Clin Microbiol* 1994;32:2307–8.
22. Hopfer RL, Perry EV, Fainstein V. Diagnostic value of cryptococcal antigen in the cerebrospinal fluid of patients with malignant disease. *J Infect Dis* 1982;145:915.
23. Bloch DA, Moses LE, Michel BA. Statistical approaches to classification. *Arthritis Rheum* 1990;33:1137–44.
24. Patterson JE, Zidouh A, Minitier P, Andriole VT, Patterson TF. Hospital epidemiologic surveillance for invasive aspergillosis: patient demographics and the utility of antigen detection. *Infect Control Hosp Epidemiol* 1997;18:104–8.
25. Francis P, Lee JW, Hoffman A, et al. Efficacy of unilamellar liposomal amphotericin B in treatment of pulmonary aspergillosis in persistently granulocytopenic rabbits: the potential role of bronchoalveolar lavage D-mannitol and galactomannan as markers of infection. *J Infect Dis* 1994;169:356–68.
26. Verweij PE, Poulain D, Obayashi T, Patterson TF, Denning DW, Ponton J. Current trends in the detection of antigenaemia, metabolites, and cell wall markers for the diagnosis and therapeutic monitoring of fungal infections. *Med Mycol* 1998;36(Suppl 1):146–55.
27. Maertens J, Verhaegen J, Demuyneck H, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis. *J Clin Microbiol* 1999;37:3223–8.
28. Einsele H, Hebart H, Roller G, et al. Detection and identification of

- fungal pathogens in blood by using molecular probes. *J Clin Microbiol* **1997**; 35:1353–60.
29. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. *Clin Infect Dis* **1992**; 15:414–21.
 30. Anaissie EJ, Rex JH, Uzun Ö, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. *Am J Med* **1998**; 104: 238–45.
 31. Berenguer J, Buck M, Witebsky F, Stock F, Pizzo PA, Walsh TJ. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis: disseminated versus single organ infection. *Diagn Microbiol Infect Dis* **1993**; 17:103–9.
 32. Lecciones JA, Lee JW, Navarro EE, et al. Vascular catheter-associated fungemia in patients with cancer: analysis of 155 episodes. *Clin Infect Dis* **1992**; 14:875–83.
 33. Edwards JE. Editorial response: should all patients with candidemia be treated with antifungal agents? *Clin Infect Dis* **1992**; 15:422–3.
 34. Walsh TJ, Hiemenz J, Pizzo PA. Evolving risk factors for invasive fungal infections: all neutropenic patients are not the same [editorial]. *Clin Infect Dis* **1994**; 18:793–8.
 35. Yu VL, Muder RR, Poorsattar A. Significance of isolation of *Aspergillus* from the respiratory tract in diagnosis of invasive pulmonary aspergillosis: results of a three-year prospective study. *Am J Med* **1986**; 81: 249–54.