Invasive fungal diseases (IFDs) have become major causes of morbidity and mortality among highly immunocompromised patients. Authoritative consensus criteria to diagnose IFD have been useful in establishing eligibility criteria for antifungal trials. There is an important need for generation of consensus definitions of outcomes of IFD that will form a standard for evaluating treatment success and failure in clinical trials. Therefore, an expert international panel consisting of the Mycoses Study Group and European Organization for Research and Treatment of Cancer convened to propose guidelines for defining responses to therapy and study outcomes in clinical trials of IFDs.

Invasive fungal diseases (IFDs) are major causes of morbidity and mortality among highly immunocompromised patients. The European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) published guidelines on definitions of IFDs for clinical research [1, 2]. Bennett et al. [3–5] previously discussed challenges in the design of antifungal trials. Our objective here is to establish consensus criteria for evaluating therapeutic responses in phase III trials of IFDs.

Although specific criteria for therapeutic success vary for the major IFDs, global response requires survival and a positive effect on fungal disease (table 1). With certain IFDs (e.g., candidemia), cure is the goal of therapy. The term, “documented clearance” is more appropriate than “sterilization,” because the yield of cultures can
varya, especially while patients are receiving antifungals. In histoplasmosis and cryptococcosis, a response soon after start of therapy may be termed, “successful control of disease,” correctly implying that cure may not have been achieved. Indeed, the best proof of cure for these fungal diseases is absence of relapse after cessation of therapy. The observation period to meet this high standard for certain IFDs may involve years and would be impractical for therapeutic trials. Therefore, we attempted to strike a balance between these limitations and practical end points that can be incorporated into therapeutic trials.

The 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. However, it is also reasonable to make provision for “success with modification,” as was done in a trial that compared voriconazole with amphotericin B therapy for invasive aspergillosis in which the protocol, in effect, evaluated 2 different treatment regimens rather than 2 different drugs [6, 7].

CONFLICTING DATA

Recognizing when primary antifungal therapy fails is often not straightforward, particularly when data are inadequate or conflicting [8–10]. Protocols should ideally prespecify a rank order of the weight given to specific categories of data, with more weight generally given to objective data (e.g., oxygen saturation) than to subjective data (e.g., presence of dyspnea), as well as to specific signs of fungal diseases (e.g., facial swelling in invasive fungal sinusitis) than to less specific signs (e.g., fever).

Discordant clinical, radiological, and/or mycological data may result from an inadequate period of evaluation. Selection of time points for assessment of response should account for the potential of early conflicting data. A competing concern is that longer periods of evaluation of response may increase the likelihood of seemingly unrelated events (e.g., relapsed malignancy) that would confound the interpretation of response to antifungal therapy. Suggested minimum periods of observation for the major IFDs are included in tables 2–5.

REQUIREMENT FOR SURVIVAL

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. Because mortality may result from causes seemingly unrelated to the IFD, some panel members argued that more-direct markers of response to antifungal treatment (e.g., clearance of cultures or a reduction in the level of a laboratory marker) should be used as primary end points instead of survival. Prespecified criteria for attributable mortality have been used in some studies of antifungals [11–13]. Anaissie [14] argued that, in patients with invasive aspergillosis (IA), deaths for which there is no autopsy evidence of persistent fungal disease should be considered successful outcomes in trials of antifungal agents.

Attribution of mortality is difficult in patients with medically complex cases [15], even for the minority for whom autopsies are performed. Drug toxicity may influence survival in ways not obvious to the investigator (e.g., drug-drug interactions) [16] or at autopsy. In addition, the interaction of antifungal drugs with host immunity is an area of growing interest [17–23]; 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 confounding variables that affect survival in the ITT or MITT analysis.

CANDIDEMIA AND OTHER FORMS OF INVASIVE CANDIDIASIS

In candidemia, documented clearance of Candida species from the blood should be a requirement for a successful outcome. Symptoms and signs (e.g., fever) attributable to disease may persist, but such signs are nonspecific and should not, by

---

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

<table>
<thead>
<tr>
<th>Outcome, response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease</td>
</tr>
<tr>
<td>Complete response</td>
<td>Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined on the basis of a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td>Partial response</td>
<td>Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td>Failure</td>
<td>Death during the prespecified period of evaluation, regardless of attribution</td>
</tr>
<tr>
<td>Stable response</td>
<td>Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td>Progression of fungal disease</td>
<td>Death</td>
</tr>
</tbody>
</table>

* In certain invasive fungal diseases (e.g., invasive mold diseases), stabilization of fungal disease during periods of severe immunocompromise provides evidence of efficacy of treatment and may be a reasonable short-term therapeutic goal until immune recovery occurs.
themselves, be equated with failure. Removal of a central line may reduce the time to clearance of blood cultures in cases of candidemia [24]. However, unless the protocol prescribes removal of intravenous catheters as a requirement for eligibility, catheter removal should not be considered in the outcome assessment. Follow-up sampling of easily accessible sites, such as CSF in patients with meningitis and persistent joint fluid in those with arthritis, should be required to evaluate therapeutic response. If follow-up samples are not obtained, the response should either be scored as indeterminate or a failure if other signs of progressive or poorly controlled disease (e.g., multiorgan failure) occur.

The time to assess primary outcomes in candidemia should not just encompass clearance of blood but also be adequate to detect early recrudescence of candidiasis and mortality directly or indirectly related to fungal disease. We suggest a period of observation of at least 4 weeks after start of therapy, because fever can result from multiple causes unrelated to candidemia, we suggest that more weight be given to documented clearance of pathogens from the blood than to resolution of fever in the global assessment of response to therapy. Thus, the scenario of persistent or recurrent fever despite clearance of blood should be assessed as at least a partial response and, therefore, equated with a successful response.

NOTE. The minimum period of observation is 4 weeks after start of therapy. The rationale for this minimum period of evaluation is to detect relapses of disease. Relapse generally requires a positive result of a culture of a specimen of blood or of another sterile site and not simply recurrence of symptoms or signs (e.g., fever) that are generally nonspecific. In the specific cases of visceral organ involvement (e.g., endocarditis, meningitis, retinitis, or chronic disseminated candidiasis), we suggest a period of observation of at least 12 weeks after start of therapy.

If additional 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.

### INVASIVE ASPERGILLOSIS AND OTHER MOLD DISEASES

Evaluation of response to therapy in invasive mold disease is difficult. In the highly immunocompromised patient, fever and localizing physical examination findings are often absent [25]. In addition, some of the clinical manifestations of IA may not necessarily indicate clinical deterioration. For example, hemoptysis is more common after neutrophil recovery [26] and may not signify refractory disease.

Evaluation of radiological responses, particularly at early time points, poses several challenges. Caillot et al. [27] performed sequential CTs on patients with neutropenia and IA. Despite administration of effective antifungal treatment, leading to a positive clinical response in most patients, the median volume of lesions increased 4-fold during the first week of therapy and remained stable during the second week. This study has implications with regard to the interpretation of results of salvage therapy in which neutropenic patients with IA could be enrolled after only 7 days of standard antifungal therapy on the basis of radiological worsening [8,..]
ing therapeutic responses, because it is poses additional challenges for interpret-
for invasive craniofacial mold disease)
eases or noninfectious diseases.
problems in assessing outcome are incorrect
diagnosis, mixed fungal diseases [25, 36],
trophil recovery may also be incorrectly
radiological response can be equated with
control of disease. Other potential prob-
for response to therapy may not be feasible
(e.g., repeated lung biopsies) to evaluate
IA in nonneutropenic patients who re-
edge about the radiological evolution of
[27, 33–35]. There is inadequate knowl-
equated with fungal disease progression
progression of disease Worsening clinical symptoms or signs of disease; plus
Persistent isolation of mold or histological presence of invasive hyphae in infected sites
New sites of disease or radiological worsening of preexisting lesions; or
Persistent isolation of mold species from infected sites
Death
Death during the prespecified period of evaluation regardless of attribution

NOTE. The minimum period of observation is at least 6 weeks in trials of primary therapy, but assessment of outcome at week 12 or later should be included as a secondary end point. For trials of salvage therapy, consider evaluation of the primary end point at least 12 weeks after enrollment.

* Clear evidence of a radiological response (reduction in diameter by at least 25% with no new sites of disease) should be given more weight than subjective, nonspecific, or difficult-to-quantify symptoms or signs of disease. Thus, in the scenario of fungal pneumonia, we suggest that radiological improvement with persistence of fever or cough should be scored as a partial response. Because radiological improvement often lags behind clinical improvement, especially if a short-term period of evaluation is employed (see Invasive Aspergillosis and Other Mold Diseases), we suggest that radiological stabilization and resolution of all attributable symptoms and signs of disease can also be equated with a partial response. See text for discussion of serum galactomannan index as a promising correlate of therapeutic outcome.

28–32]. Cavitation coinciding with neu-
and coexistent bacterial and fungal dis-
...successfully and with a complete radiological response; plus
...clear evidence of a radiological response (reduction in diameter by at least 25% with no new sites of disease) should be given more weight than subjective, nonspecific, or difficult-to-quantify symptoms or signs of disease. Thus, in the scenario of fungal pneumonia, we suggest that radiological improvement with persistence of fever or cough should be scored as a partial response. Because radiological improvement often lags behind clinical improvement, especially if a short-term period of evaluation is employed (see Invasive Aspergillosis and Other Mold Diseases), we suggest that radiological stabilization and resolution of all attributable symptoms and signs of disease can also be equated with a partial response. See text for discussion of serum galactomannan index as a promising correlate of therapeutic outcome.

Defining Responses to Antifungal Therapy • CID 2008;47 (1 September) • 677
Table 4. Responses to antifungal therapy in cryptococcal meningitis.

<table>
<thead>
<tr>
<th>Outcome, response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>Survival and resolution of all attributable symptoms and signs of disease; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of pathogen from CSF; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of pathogen from blood in cases of bloodstream disease; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of pathogen from other sites of disease (if additional cultures are performed); plus</td>
</tr>
<tr>
<td></td>
<td>Improvement or stabilization of radiological lesions if present [e.g., CNS cryptococcoma]</td>
</tr>
<tr>
<td>Partial response</td>
<td>Survival and improvement of attributable symptoms and signs of disease; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of pathogen from CSF; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of pathogen from blood in cases of bloodstream disease; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of pathogen from other sites of disease if additional cultures are performed; plus</td>
</tr>
<tr>
<td></td>
<td>Improvement or stabilization in radiological lesions if present at baseline</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td></td>
</tr>
<tr>
<td>Stable response</td>
<td>Survival and minor or no improvement in attributable symptoms and signs of disease; plus</td>
</tr>
<tr>
<td></td>
<td>Persistently positive results of cultures of CSF specimens or specimens of other infected sites</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>Persistently positive results of cultures of CSF specimens or specimens of other infected sites plus</td>
</tr>
<tr>
<td></td>
<td>New sites of disease or worsening of preexisting lesions radiologically</td>
</tr>
<tr>
<td>Death</td>
<td>Death during the prespecified period of evaluation, regardless of attribution</td>
</tr>
</tbody>
</table>

**NOTE.** The minimum period of observation is 10 weeks after the time of initiation of study drug. The rationale for this minimum period of evaluation is that assessments of clinical and mycological responses may conflict at early time points.

Invasive mold diseases, the overall rate of concordance between treatment responses assessed at 1 and 3 months was only 42% (C. Hardalo, Schering-Plough, personal communication). The concordance between 3- and 6-month assessments showed substantial improvement (76%). For primary therapy trials of IA, most of the panel members considered 6 weeks after enrollment to be the minimum time to assess the primary outcome end point. An analysis at week 12 or later should be included as a secondary end point. By extrapolation, this period of observation is reasonable for non-*Aspergillus* invasive mold diseases. In salvage studies, a time point of at least 12 weeks should be considered for the primary end point analysis.

**CRYPTOCOCCAL MENINGITIS**

*C. neoformans* disease most commonly manifests as meningitis. Assessment of treatment response in cryptococcal meningitis relies on clinical and mycological criteria [46–48]. Documented clearance of CSF typically precedes the expected reduction in antigen titers in patients with a response to antifungal therapy [46] and is the “gold standard” to evaluate mycological response. CSF specimens obtained by lumbar puncture are likely to be more sensitive for recovery of organisms than are those obtained by intraventricular collection; if the initial lumbar fluid specimen yields positive results followed by a negative ventricular fluid specimen, no conclusion should be drawn. Clearance of CSF is given more weight than clinical criteria (e.g., fever and meningismus) in assessing the global response. Thus, clearance of CSF but persistence of fever or headache should be equated with at least a partial response.

IRIS results from an exuberant inflammatory response toward previously diagnosed infection or infection with incriminating pathogens (e.g., mycobacterial and cytomegalovirus disease). IRIS is well described in patients with AIDS-associated cryptococcal meningitis after initiation of antiretroviral therapy and manifests with meningismus and elevated CSF opening pressures, protein levels, and WBC counts.
Table 5. Responses to antifungal therapy in systemic histoplasmosis.

<table>
<thead>
<tr>
<th>Outcome, response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>Survival and resolution of all attributable symptoms and signs of disease; plus Resolution of radiological lesion(s); 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 (e.g., blood and CSF) If infected sites are not accessible to repeat sampling for cultures, clearance of Histoplasma antigen from serum and urine (if detected at baseline) can be used as a mycological criterion for complete response.</td>
</tr>
<tr>
<td>Partial response</td>
<td>Survival and improvement of attributable symptoms and signs of disease; plus Improvement in radiological lesions; plus Documented clearance of infected sites that are accessible to repeated sampling (e.g., blood and CSF) If infected sites are not accessible to repeated sampling for cultures, a decrease in the serum Histoplasma antigen level of at least 50% during the first 3 months of therapy, relative to the baseline level, can be equated with a partial mycological response</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td></td>
</tr>
<tr>
<td>Stable response</td>
<td>Survival and minor or no improvement in attributable symptoms and signs of disease; plus Radiological stabilization; or Persistently positive results of cultures of specimens from infected sites; or</td>
</tr>
<tr>
<td></td>
<td>If infected sites are not accessible to repeated sampling for culture, lack of a decrease in the serum Histoplasma antigen level of at least 50% after 3 months of therapy can be equated with a stable mycological response</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>Worsening clinical symptoms or signs of disease; plus New sites of disease or radiological worsening of preexisting lesions; or Persistently positive results of cultures of specimens from infected sites; or</td>
</tr>
<tr>
<td></td>
<td>If infected sites are not accessible to repeated sampling for cultures, an increase in the serum Histoplasma antigen level of &gt;20% can be a mycological criterion for worsening of disease</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>Death during the prespecified period of evaluation, regardless of attribution</td>
</tr>
</tbody>
</table>

**NOTE.** Three months from time of initiation of study drug is a suggested minimum period of observation for systemic histoplasmosis. Because some patients develop relapsed disease while receiving antifungal therapy, assessment of outcome at 12 months after initiation of study drug is suggested as a secondary end point.

[49–51]. Repeated CSF cultures are required to distinguish IRIS from persistent or recrudescent cryptococcal disease. IRIS does not represent treatment failure.

In CNS cryptococcal disease, neurological sequelae, such as blindness and dementia, can persist indefinitely and are not due to persistent microbes. The absence of fungal disease would meet the mycological end point for a successful outcome and, in fact, could be equated with cure of disease. However, the majority of panel members considered a measurable clinical improvement to be a requisite for a successful outcome in cases of cryptococcal meningitis. This approach is consistent with use of primary end points for therapeutic trials of bacterial meningitis that include neurological sequelae [52–57].

Repeated sampling of CSF is required to assess the therapeutic response, because clinical symptoms may not correlate with control of disease. Use of systemic corticosteroids and other immunosuppressive agents may blunt symptoms and signs of meningitis. If an additional CSF sample is not obtained, then the outcome should be scored as “indeterminate” if a clinical response occurs and as “failure” if clinical findings are unchanged or worsen. In cases of concurrent extraneural C. neoformans disease, a mycological response involves documented clearance of disease from involved sites if repeated sampling is feasible (e.g., blood cultures for fungemic patients).

Brouwer et al. [58] evaluated antifungal regimens in patients with AIDS-associated cryptococcal meningitis, using the rate of reduction in CSF colony-forming units within the first 2 weeks as the primary end point. Despite the low number of subjects, this study identified amphotericin B plus flucytosine as the most effective regimen.

In phase I/II studies in which patient accrual is limited, such quantitative mycological end points provide valuable data. However, definitive phase III trials should include longer-term end points and be adequately powered to evaluate survival, persistent morbidity, and drug toxicity.

**ENDEMIC MYCOSES**

Our guidelines focus on disseminated histoplasmosis and coccidioidomycosis. Chronic fibrocavitary forms of pulmonary histoplasmosis and coccidioidomycosis may show little radiological improvement with successful drug therapy. In meningitis, clinical and mycological evidence of control of disease are requisites of a successful global response. Radiological res-
olution of CNS fungal lesions is rarely complete, even after years of observation. Improvement of CT and MRI findings is a more useful end point to judge success, with the caveat that improvement in edema can be associated with corticosteroid therapy. IRIS has been reported in patients with AIDS-associated histoplasmosis receiving antiretroviral therapy [59] and does not denote treatment failure.

**Histoplasmosis.** Clearance of blood cultures is the gold standard for mycological response in patients with histoplasmosis and positive blood culture results. However, blood cultures, including those that undergo lysis-centrifugation, are too insensitive for results to be used as the sole criterion to evaluate success. Culture results may be negative before commencement of therapy and may yield only intermittently positive results during unsuccessful therapy. Thus, clearance of positive blood cultures is necessary, but not sufficient, to determine whether an outcome is successful.

Nonculture laboratory markers are useful adjuncts in monitoring the response to systemic histoplasmosis, with the provision that these tests should be conducted using the same method and ideally in the same reference laboratory. Although results of the *Histoplasma* antigen test has not been used as a study end point in clinical trials, changes in antigen findings have paralleled those of culture in patients with positive culture results [60–62]. In patients with histoplasmosis and positive blood culture results, clearance of fungemia is a better measure of antifungal effect than is clearance of antigen [63]. However, reduction in antigen levels could be used as a mycological end point in patients with negative blood culture results and as additional evidence of response in patients with positive culture results. Using a conservative measure, a decrease in the serum antigen level by at least 50% during the first 3 months of therapy relative to the baseline level can be equated with a positive mycological response. In patients whose antigen levels have decrease with therapy, a subsequent increase of ≥20% raises concern about relapse [64]. Antigen levels were evaluated principally in AIDS-associated disseminated histoplasmosis; the predictive value of therapeutic response in other patient populations has not been established. Antigen levels in urine may not decrease for several weeks, even with effective therapy [65]; therefore, persistent antigenuria should not be equated with failure of therapy.

**Coccidioidomycosis.** Several trials of coccidioidomycosis used a composite scoring system to assess therapeutic response [66–70]. Points were assigned on the basis of (1) symptoms, (2) physical examination findings, (3) quantitative complement fixation titers (baseline and follow-up titers measured in the same laboratory concurrently), and (4) culture results. Numerical values were assigned on the basis of prespecified rules, and the sum of these values at reassessment was compared with baseline values, with an increasing score indicating deterioration. A successful response required a >50% reduction in abnormal baseline findings ≤8 months after commencement of therapy.

For patients with CNS coccidioidomycosis, life-long azole therapy is standard because of the high frequency of recrudescence disease if therapy is stopped [71, 72]. A composite numeric outcome score using clinical and laboratory abnormalities has been applied to coccidoidal meningitis [73, 74]. In one study, a response was defined as a >40% reduction in baseline abnormalities without subsequent relapse during antifungal treatment [73]. A patient who had not achieved this level of improvement after 8 months was considered to be a nonresponder. For coccidoidal meningitis, CSF specimens obtained by lumbar puncture are likely to be more sensitive for recovery of organisms than are those obtained by intraventricular collection; if the initial lumbar fluid specimen yields a positive result followed by a negative ventricular fluid result, no conclusion should be drawn. Moreover, except in the rare patient with ventriculitis, ventricular fluid findings may provide an overly optimistic picture of the status of the coccidoidal disease, with lower cell counts, protein levels, and antibody titer levels and higher glucose values, compared with lumbar or cisternal fluid specimens; this could be misleading if the scoring system does not repeatedly evaluate the same CSF compartment.

Chronic soft-tissue, bone, and pulmonary disease are also characteristic of coccidioidomycosis. Some of the original antifungal salvage therapy trials involved patients with persistent coccidioidomycosis [75]. Therefore, in trials of these forms of coccidioidomycosis, improvement of clinical and laboratory end points during therapy without eradication of disease may fulfill the criteria for a successful outcome. A minority of patients with coccidioidomycosis may require ≥9 months to respond to antifungal therapy [76]; therefore, extension of the time to evaluate the primary end point to, for example, 12 months is expected to change the outcome for this subset of patients.

**FUTURE PERSPECTIVES**

To enhance trial efficiency, the US Food and Drug Administration recommended use of surrogate markers that can substitute for clinical events as tools to increase diagnostic specificity and to provide objective outcome measures [77]. Future trials involving IFDs—particularly mold diseases—should include validation of laboratory assays as predictive correlates of outcome. Such studies will ideally include prespecified serial monitoring of the marker of interest measured at the same reference laboratory. Future development and validation of sensitive, non–culture-based laboratory assessments (e.g., PCR) and, potentially, functional imaging modalities (e.g., positron emission tomography [78]) may facilitate both the early diagnosis of IFD and the assessment of therapeutic response.
Acknowledgments

Potential conflicts of interest. B.H.S. has served on speakers’ boards for Merck and Pfizer and on advisory committees for Pfizer, Berlex, and Schering Plough. B.E.d.P. has served on speakers’ boards for Gilead, Merck, and Pfizer and on the advisory board for Basilea Pharmaceutical. J.R.G. has served on advisory boards for Merck and Schering-Plough, Pfizer, Astellas, Enzon, and Merck. C.A.K. has served on speakers’ boards for or received research grants from Merck, Schering-Plough, and Astellas. L.O.-Z. has received research grants from Astellas, Merck, Pfizer, Associates of Cape Cod, and Rockeye and has served on speakers’ boards for Astellas, Merck, Pfizer, Enzon, and Gilead. J.R.W. has served as a consultant for Merck, Pfizer, and Schering-Plough and has served on the speakers’ boards for or received honoraria from Merck, Pfizer, Schering-Plough, and MGI Pharma. J.R.G. has served on the speakers’ board for Merck for two years. J.R.W. has received research funding from Merck and Schering-Plough; has served as a consultant for Merck, Schering-Plough, Pfizer, F2G, and Nektar; and has served on the advisory board for Schering-Plough. D.A.S. has served on advisory boards for Enzon and Gil-ead. I.J.W. is the President of MiraVista Diagnostics/MiraBella Technologies, which manufactures Histoplasma and Aspergillus antigen tests. E.I.B. has received research grants from Pfizer, Schering-Plough, Astellas, Wyeth, and Amgen and has worked as a consultant for Pfizer, Schering-Plough, Astellas, Wyeth, and Amgen. J.S. has received re- search grants from Pfizer, Merck, and has served on advisory boards for Merck and Pfizer; and has served on speakers’ boards for Merck, Pfizer, and Schering-Plough. C.C. has received research grants from Pfizer, Merck Sharp & Dohme-Chibret, Gil-ead, and Schering-Plough and has served as a con- sultant for Gilead, Schering-Plough, and Zeneus Pharma. C.V. has served on speakers’ boards for Merck, Pfizer, Schering-Plough, and Gilead; has served on advisory boards for Merck, Pfizer, Schering-Plough, and Astellas; and has received research grants from Gilead, Abbott, Bo- eheringer-Inghelheim, and Pfizer. P.G.P. has served research grants from Merck, Pfizer, SPRI, Pfizer, Astellas, Novartis, and Ei- sai. J.M. has served on advisory boards for Pfizer, Gilead, Merck Sharp & Dohme-Chibret, Schering-Plough, Zeneus, and Astellas. B.-J.K. has served as a con- sultant for Basilea, F2G, Novartis, Pfizer, and Schering-Plough and has served on speakers’ boards for MSD, Pfizer, and Schering-Plough. T.E.P. has served as a consultant for Merck, Pfizer, Schering-Plough, Basilea, Nektar Therapeutics, and Stiefel Laboratories and has served on speakers’ boards for Merck and Pfizer. T.C. has received research grants from Merck Sharp & Dohme-Chibret, Essex Schering, Roche Diagnostics, Wako, and BioRad and has served as a consultant for Merck Sharp & Dohme-Chibret, Pfizer, Novartis, Essex Scher- ing, Roche Diagnostics, and Cephalon. B.D. has served as a consultant for Schering-Plough, As- telas, Merck, Valeant, and BioAlliance. All other authors: no conflicts.

References

plete remission. A retrospective study and re-
view of the literature. Ginecma Infection Pro-
gram (Gruppo Italiano Malattie Ematologiche
27. Caillot D, Couallier JF , Bernard A, et al. In-
creasing volume and changing characteristics of
invasive pulmonary aspergillosis on se-
quential thoracic computed tomography scans
28. Viscoli C. Combination therapy for invasive
29. Marr KA, Boechl M, Carter RA, Kim HW,
Corey L. Combination antifungal therapy for
39: 797–802.
and safety of caspofungin for treatment of in-
vasive aspergillosis in patients refractory to or
intolerant of conventional antifungal therapy.
31. Perfect JR, Marr KA, Walsh TJ, et al. Vori-
conazole treatment for less-common, emerg-
ing, or refractory fungal infections. Clin Infect
32. Walsh TJ, Raad I, Patterson TF, et al. Treat-
ment of invasive aspergillosis with posacon-
azole in patients who are refractory to or in-
tolerant of conventional therapy: an externally
33. Potente G. CT findings in fungal opportunist-
ic pneumonia: body and brain involvement.
34. Gefter WB, Albelda SM, Talbot GH, Gerson
SL, Cassileth PA, Miller WT. Invasive pul-
monary aspergillosis and acute leukemia: lim-
itations in the diagnostic utility of the air cres-
35. Albelda SM, Talbot GH, Gerson SL, Miller
WT, Cassileth PA. Pulmonary cavitation and
massive hemoptysis in invasive pulmonary as-
pergillosis: influence of bone marrow recovery
in patients with acute leukemia. Am Rev Res-
funginal infections in patients with hematologic
malignancies in a tertiary care cancer center: an
autopsy study over a 15-year period
37. Maertens J, Verhaegen J, Lagrou K, Van Eldere
J, Boogaerts M. Screening for circulating gal-
actomannan as a noninvasive diagnostic tool
for invasive aspergillosis in prolonged neutro-
penic patients and stem cell transplantation
recipients: a prospective validation. Blood
aspergillosis in allogeneic stem cell transplant
recipients: increasing antigenemia is associated
with progressive disease. Clin Infect Dis
2002; 34:939–43.
Detection of circulating Aspergillus fumigatus
galactomannan: value and limits of the Platêla
test for diagnosing invasive aspergillosis. J Clin
40. Salonen J, Lehtonen OP, Terasarvi MR, Ni-
koskelainen J. Aspergillus antigen in serum,
urine and bronchoalveolar lavage specimens
of neutropenic patients in relation to clinical
41. Woods G, Miceli MH, Grazziutti ML, Zhao
W, Barlogie B, Anaisie E. Serum Aspergillus
galactomannan antigen values strongly cor-
relate with outcome of invasive aspergillosis:
a study of 36 patients with hematologic cancer.
reconstitution inflammatory syndrome in
cancer patients with pulmonary aspergillosis
receiving from neutropenia: proof of prin-
ciple, description, and clinical and research
43. Pfeiffer CD, Fine JP, Saldañ Diagnosis of
invasive aspergillosis using a galactomannan
42:1417–27.
44. Odabasi Z, Mattuzzi G, Estey E, et al. β-D-
glucan as a diagnostic adjunct for invasive fun-
gal infections: validation, cutoff development,
and performance in patients with acute mye-
logenous leukemia and myelodysplastic syn-
45. 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
46. van der Horst CM, Saag MS, Cloud GA, et al.
Treatment of cryptococcal meningitis associ-
ated with the acquired immunodeficiency syn-
drome. National Institute of Allergy and In-
fected Diseases Mycoses Study Group and
47. Woods G, Miceli MH, Grazziutti ML, Zhao
W, Barlogie B, Anaisie E. Serum Aspergillus
galactomannan antigen values strongly cor-
relate with outcome of invasive aspergillosis:
a study of 36 patients with hematologic cancer.
48. Perfect JR, Marr KA, Walsh TJ, et al. Vori-
conazole treatment for less-common, emerg-
ing, or refractory fungal infections. Clin Infect
49. Walsh TJ, Raad I, Patterson TF, et al. Treat-
ment of invasive aspergillosis with posacon-
azole in patients who are refractory to or in-
tolerant of conventional therapy: an externally
50. Potente G. CT findings in fungal opportunist-
ic pneumonia: body and brain involvement.
51. Gefter WB, Albelda SM, Talbot GH, Gerson
SL, Cassileth PA, Miller WT. Invasive pul-
monary aspergillosis and acute leukemia: lim-
itations in the diagnostic utility of the air cres-
52. Albelda SM, Talbot GH, Gerson SL, Miller
WT, Cassileth PA. Pulmonary cavitation and
massive hemoptysis in invasive pulmonary as-
pergillosis: influence of bone marrow recovery
in patients with acute leukemia. Am Rev Respir
funginal infections in patients with hematologic
malignancies in a tertiary care cancer center: an
autopsy study over a 15-year period
54. Maertens J, Verhaegen J, Lagrou K, Van Eldere
J, Boogaerts M. Screening for circulating gal-
actomannan as a noninvasive diagnostic tool
for invasive aspergillosis in prolonged neutro-
penic patients and stem cell transplantation
recipients: a prospective validation. Blood
aspergillosis in allogeneic stem cell transplant
recipients: increasing antigenemia is associated
with progressive disease. Clin Infect Dis
2002; 34:939–43.
Detection of circulating Aspergillus fumigatus
galactomannan: value and limits of the Platêla
test for diagnosing invasive aspergillosis. J Clin
57. Salonen J, Lehtonen OP, Terasarvi MR, Ni-
kkoskelainen J. Aspergillus antigen in serum,
urine and bronchoalveolar lavage specimens
of neutropenic patients in relation to clinical
58. Perfect JR, Marr KA, Walsh TJ, et al. Vori-
conazole treatment for less-common, emerg-
ing, or refractory fungal infections. Clin Infect
59. Walsh TJ, Raad I, Patterson TF, et al. Treat-
ment of invasive aspergillosis with posacon-
azole in patients who are refractory to or in-
tolerant of conventional therapy: an externally
60. Potente G. CT findings in fungal opportunist-
ic pneumonia: body and brain involvement.
61. Gefter WB, Albelda SM, Talbot GH, Gerson
SL, Cassileth PA, Miller WT. Invasive pul-
monary aspergillosis and acute leukemia: lim-
itations in the diagnostic utility of the air cres-