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

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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 designing 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...
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></td>
</tr>
<tr>
<td>Complete response</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>Partial response</td>
<td>Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, assessed by a quantitative and validated laboratory marker</td>
</tr>
<tr>
<td>Failure</td>
<td></td>
</tr>
<tr>
<td>Stable 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>Progression of fungal disease</td>
<td>Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td>Death</td>
<td>Death during the prespecified period of evaluation, regardless of attribution</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.

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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 the time of enrollment (Table 2). In the view of most of the panel members, end-of-therapy response should be avoided as a primary end point, because the time to stop therapy can be variable, and end-of-therapy successes will not capture early relapses after discontinuation of therapy.

### Table 2. Responses to antifungal therapy in patients with candidemia and other forms of invasive candidiasis.

<table>
<thead>
<tr>
<th>Outcome, response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>Complete response: Survival and resolution of all attributable symptoms and signs of disease; plus documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF).</td>
</tr>
<tr>
<td>Partial response</td>
<td>Survival and improvement of attributable symptoms and signs of disease; plus documented clearance of blood in cases of candidemia; plus documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF).</td>
</tr>
<tr>
<td>Failure</td>
<td>Stable response: Survival and minor or no improvement in attributable symptoms and signs of disease; plus persistent isolation of Candida species from blood specimens or specimens from other sterile sites; or documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF).</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>Persistent isolation of Candida species from blood specimens or specimens from other sterile sites in association with worsening clinical symptoms or signs of disease (e.g., septic shock, progression of hematogenous cutaneous candidiasis); or new sites of disease or worsening of preexisting lesions radiologically (e.g., those observed in chronic disseminated candidiasis) in association with clinical deterioration.</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 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. "Fever without localizing symptoms or other abnormal physical examination findings is the most common manifestation of candidemia. However, 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."

"In visceral candidiasis (e.g., hepatosplenic candidiasis) with negative blood culture results at baseline, persistent fever may be the only attributable symptom. Persistent fever may be the only attributable clinical sign of candidiasis, and radiological abnormalities can persist for prolonged periods. In such situations, resolution of fever and stable radiological disease may be equated with a partial response. Laboratory markers, such as PCR and the (1→3)-β-D-glucan assay, have not been adequately validated as markers of response to therapy for invasive candidiasis."
ing therapeutic responses, because it poses additional challenges for interpreting radiological responses. Invasive craniofacial mold disease may be incorrectly equated with fungal disease progression [27, 33–35]. There is inadequate knowledge about the radiological evolution of IA in nonneutropenic patients who respond to antifungal therapy.

Repeated sampling of infected sites (e.g., repeated lung biopsies) to evaluate response to therapy may not be feasible or clinically warranted. In such cases, radiological response can be equated with control of disease. Other potential problems in assessing outcome are incorrect diagnosis, mixed fungal diseases [25, 36], and coexistent bacterial and fungal diseases or noninfectious diseases.

Surgery as a therapeutic modality (e.g., for invasive craniofacial mold disease) poses additional challenges for interpreting therapeutic responses, because it is generally not possible to judge the effect of drug treatment alone. We suggest judging success or failure at the prespecified time of analysis, without considering whether surgery was performed. In a secondary analysis, patients treated with drug alone versus the drug plus surgery may be analyzed separately.

In addition to facilitating the diagnosis of IA, the galactomannan assay is also a promising therapeutic marker [13, 37–40]. Boutboul et al. [38] showed that serum galactomannan index (GMI) values significantly increased in patients with IA who did not respond to antifungal therapy, whereas no significant change occurred in patients who responded to therapy. Maertens et al. [37] reported that all 24 patients with IA who subsequently cleared fungal disease without a change in therapy demonstrated the utility of serial GMI testing as a predictor of outcome in patients with multiple myeloma and IA. Miceli et al. [42] defined immune reconstitution inflammatory syndrome (IRIS) as clinical and radiological deterioration and reduction in serum GMI values coinciding with neutrophil recovery in patients with IA who subsequently cleared fungal disease without a change in therapy. Serum GMI has better performance as a diagnostic marker in patients with hematological malignancies and allogeneic hematopoietic stem cell transplant recipients than in solid-organ transplant recipients [43], suggesting that its utility as a therapeutic marker may also be influenced by host factors.

Anaissie [14] argued that serum GMI values should be used both in practice and in clinical trials as an early marker of ther-
The majority of panel members considered serial GMI measurements to be a highly promising therapeutic marker but believed that it was currently premature to adopt serum GMI value as a primary mycological end point in clinical trials of IA; serum GMI monitoring should be included as a secondary end point. Serum \((1\rightarrow3)-\beta-D\)-glucan can be a valuable diagnostic adjunct in a number of IFDs, including invasive candidiasis and aspergillosis [2, 44, 45]. Data on the utility of serum \((1\rightarrow3)-\beta-D\)-glucan monitoring as a therapeutic marker are limited.

Clinical, radiological, and mycological end points may conflict, particularly at early time points [9, 10]. In the study comparing voriconazole with amphotericin B as primary therapy for IA, the difference in successful outcomes was apparent by 6 weeks [6]. Most deaths (50 [68%] of 73) that occurred during the first 6 weeks were attributable to IA; of the 25 deaths during the second 6 weeks, only 6 (24%) were attributed to IA [11]. However, in 2 pooled trials (P041 and P02387) that evaluated posaconazole as salvage therapy for 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 incubating 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>Success Complete response</td>
<td>Survival and resolution of all attributable symptoms and signs of disease; plus</td>
</tr>
<tr>
<td></td>
<td>Resolution of radiological lesion(s); persistence of only a scar or postoperative changes can be equated with a complete radiological response; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of infected sites that are accessible to repeated sampling (e.g., blood and CSF)</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Improvement in radiological lesions; plus</td>
</tr>
<tr>
<td></td>
<td>Documented clearance of infected sites that are accessible to repeated sampling (e.g., blood and CSF)</td>
</tr>
<tr>
<td></td>
<td>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>Failure Stable response</td>
<td>Survival and minor or no improvement in attributable symptoms and signs of disease; plus</td>
</tr>
<tr>
<td></td>
<td>Radiological stabilization; or</td>
</tr>
<tr>
<td></td>
<td>Persistently positive results of cultures of specimens from infected sites; or</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>Worsening clinical symptoms or signs of disease; plus</td>
</tr>
<tr>
<td></td>
<td>New sites of disease or radiological worsening of preexisting lesions; or</td>
</tr>
<tr>
<td></td>
<td>Persistently positive results of cultures of specimens from infected sites; or</td>
</tr>
<tr>
<td>Death</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 coccidioidal 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 coccidioidal 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 assays (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.
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References


