Learning from Our Failures: The Antifungal Treatment Conundrum

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(See the article by Nucci and Perfect on pages 1426–33)

It is often said that we learn more from our failures than from our successes. Certainly, there is truth to this adage with regard to antifungal therapy. There is much for us to learn from antifungal treatment failure.

Although it is hard to accept failure, all too often, it is even harder to recognize failure in antifungal therapy. Clinical and radiological criteria of treatment response are flawed by considerable subjectivity, and they have not been well validated in clinical studies. The criteria commonly used in clinical practice and in clinical trials have been developed largely from the judgments of “experts.” Although such criteria are well reasoned, they are imprecise, and sometimes, reliance on such criteria may unwittingly mislead us. Clinical deterioration often occurs as immune reconstitution in the host occurs, which, ironically, is one of the most important facets of ultimate recovery and therapy success, not failure. This has been observed in cryptococcal meningitis in several different types of patients [1–3].

Moreover, radiological studies of tissue-invasive fungal infections, such as invasive aspergillosis, show that infiltrate attributable to the infection typically worsen during treatment before eventual improvement; such “worsening” is as much attributable to host inflammation as to microbial activity [4, 5].

Are microbiological indicators of response much better? Results of follow-up cultures of blood samples from patients with bloodstream or disseminated fungal infections may be negative during therapy, yet these results do not reliably indicate microbial eradication in deep tissues. Moreover, serial cultures are often not an option for judging the microbiological status of deep-tissue infections, because invasive tests to obtain tissue samples at repeated intervals are not practical.

Why does antifungal treatment failure occur? One obvious reason may be that antimicrobial resistance and failure attributable to drug resistance clearly do occur. But there is a gap between the numbers of instances in which resistant fungal pathogens are isolated before or during the course of therapy (relatively infrequent) and the numbers of instances of treatment failures (much more frequent). This gap indicates that many therapy failures are not attributable to drug resistance. A drug may fail even when it is active against the pathogen if there are insufficient drug concentrations systemically or at the site of infection; certainly, this may account for some of this gap between drug resistance and treatment failure.

Yet, in many instances of treatment failure, the host may be responsible for treatment failure. In the absence of some measure of host defenses (more than a modicum) to fight infection, no antifungal drug will keep an invasive infection at bay for long. Unfortunately, criteria of attribution of treatment failure to either the drug or the host are not well developed, and criteria are certainly not well validated. Again, we rely on expert opinion all too often to arbitrate this in the context of clinical trials.

How long should a clinician wait to see whether response is occurring, and what are the optimal criteria by which a clinician should judge success and failure? Waiting too long is bad: if the infection is too far advanced, a midcourse corrective action is unlikely to succeed. Being precipitous in declaring failure is also bad: abandoning effective first-line therapy needlessly is risky, because the prospect for success with a second-line therapy is likely to be lower (or the treatment more toxic), and if an investigational therapy is chosen, the prospects are uncertain at best. Moreover, we may attribute the eventual success to the “salvage” therapy when it was actually the primary therapy that set the stage for recovery, although the salvage therapy was initiated before
it was possible to detect the response to the first therapy.

In the article by Nucci and Perfect (in this issue [6]), these issues are nicely laid out, and the various nuances are discussed. The article offers practical suggestions, step by step, for clinicians to consider as they assess treatment response and what to do next.

The first step of learning is recognition of what we do not know. Clearly, our current tools to assess treatment response have enormous shortcomings. With today’s lack of reliable microbiological surrogate markers that can quantify pathogen burden (along the line of those for HIV) for serial assessment during therapy, we must rely on a mixture of clinical, radiological, and laboratory parameters for assessment of response or failure. When all of these signals are congruent in pointing toward improvement, the assessment seems obvious and not difficult. What is more difficult and all too common, is assessment when there is divergence among these signals: the patient appears clinically worse but the culture result is now negative, or images indicate that the pulmonary infiltrate is worse but the patient is clinically better. Such is the familiar conundrum of antifungal treatment assessment.

The stakes for assessing treatment response correctly are high. We face these daunting treatment decisions every day in the clinic and must make difficult decisions on the basis of imprecise data. Implications for the design and interpretation of clinical intervention trials are similarly huge. The decision about when and how to characterize success (and failure) of primary therapy has varied considerably from trial to trial, and these differences influence how we should interpret the finding of the specific trial and how clinicians should apply the lessons to treatment of patients who may not have met the restrictive eligibility criteria of those included in the trial. The decision about how to interpret the usefulness of a salvage therapy is extremely difficult because of the considerations named above and is highly reliant on how and when first-line therapy was declared a failure and whether that determination was based on valid criteria. Can we even reliably interpret the value of salvage therapy with so much uncertainty?

Surrogate markers of microbial burden assessed serially during treatment may hold the key to the future. Although there are few that have been adequately studied and found to be reliable (except in certain instances), there are promising prospects: new imaging strategies (e.g., positron emission tomography imaging) may be able to distinguish between metabolically active processes and inactive scars on CT images. Although this may prove (with more testing) to be more sensitive than current radiological imaging, it is not specific. Perhaps using fungal tags with imaging techniques may be even more useful. More work with fungal biomarkers is needed. Results of recent work with galactomannan testing during therapy suggest promise for monitoring Aspergillus therapy in neutropenic patients with cancer [7]. The use of PCR assays for monitoring fungal therapy is in its infancy. Although enormous promise is at hand, the development of PCR assays for fungal species such as Aspergillus species is fraught with considerable difficulty, because of widespread environmental contamination and difficulty in DNA extraction [8] that must be overcome before this technique can be used with reliable results.

Therefore, there is much to learn from our failures. Only by embracing failure and trying to learn from this conundrum can we move forward, to lessen the likelihood of future failure.

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References