REVIEW ARTICLE

When Primary Antifungal Therapy Fails

Marcio Nucci[1] and John R. Perfect[2]

[1]University Hospital, Universidade Federal do Rio de Janeiro, Brazil; and [2]Department of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina

(See the editorial commentary by Wingard on pages 1434–5)

The prognosis for persons with invasive fungal infections has improved over the past 2 decades because of the development of new diagnostic tools, a better understanding of the epidemiology and prognostic factors of these infections, and the availability of new antifungal agents. Nevertheless, antifungal therapy failure is still a substantial clinical problem. When this occurs, the clinician is tempted to attribute therapeutic failure to specifi drug resistance and then to change therapy or add another antifungal drug to the regimen. However, other factors may play an even greater role in antifungal therapy failure, such as host factors, low concentration of the drug at the site of infection, drug toxicities, wrong diagnosis, and misdiagnosis of failure because of the occurrence of immune reconstitution inflammato y syndrome. In this review, we discuss the differential diagnosis and management of antifungal therapy failure in invasive mycoses, to help clinicians appreciate the meaning of primary antifungal therapy failure.

Invasive fungal infections (IFIs) have become a major complication in medical practice; they occur in different clinical contexts, such as hematopoietic stem cell transplantation, solid organ transplantation, cancer, and AIDS, as well as severely ill patients hospitalized in intensive care units and neonates [1]. IFIs have a major impact on outcome, both in terms of morbidity and mortality. Paralleling the increased incidence of IFIs, new therapeutic antifungal options have become available since the 1990s, including the lipid preparations of amphotericin B, new azoles, and the echinocandins [2]. The availability of these new agents, a better understanding of the epidemiology and prognostic factors of these infections, and the development of new diagnostic tools have contributed to an improvement in the management of IFIs. However, even with these advances, therapy failure is still a substantial clinical problem [3], occurring in 20%–60% of patients with invasive candidiasis [4–11], in 40%–70% of patients with invasive aspergillosis (IA) [12–15], and in 30%–100% of patients with invasive fusariosis [16]. These figu es may vary, depending on the definitio of failure, progress of underlying disease, and specifi patient population, but whatever the most accurate figu e, antifungal treatment failure rates remain substantial.

When antifungal therapy fails, the clinician may be tempted to attribute failure to specifi drug resistance and then may change therapy or add another antifungal drug to the regimen. However, direct resistance of a fungal strain to antifungal drugs represents only 1 explanation for therapy failure, and other factors related to the host's underlying disease and/or immune status, drug pharmacokinetics, and pharmacodynamics may play an even greater role. Therefore, we reviewed the incidence, differential diagnosis, and management of antifungal therapy failure in treatment of IFIs, to help clinicians appreciate the importance of primary antifungal therapy failure.

DEFINITION OF ANTIFUNGAL TREATMENT FAILURE

Antifungal treatment failure should be considered in any patient who presents with clinical progression of an IFI despite the use of antifungal therapy. However,

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Reprints or correspondence: Dr. Marcio Nucci, Hospital Universitário Clementino Fraga Filho, Rua Professor Rodolpho Paulo Rocco, 255 21941-913 Rio de Janeiro, Brazil (mnucci@hucff.ufrj.br).

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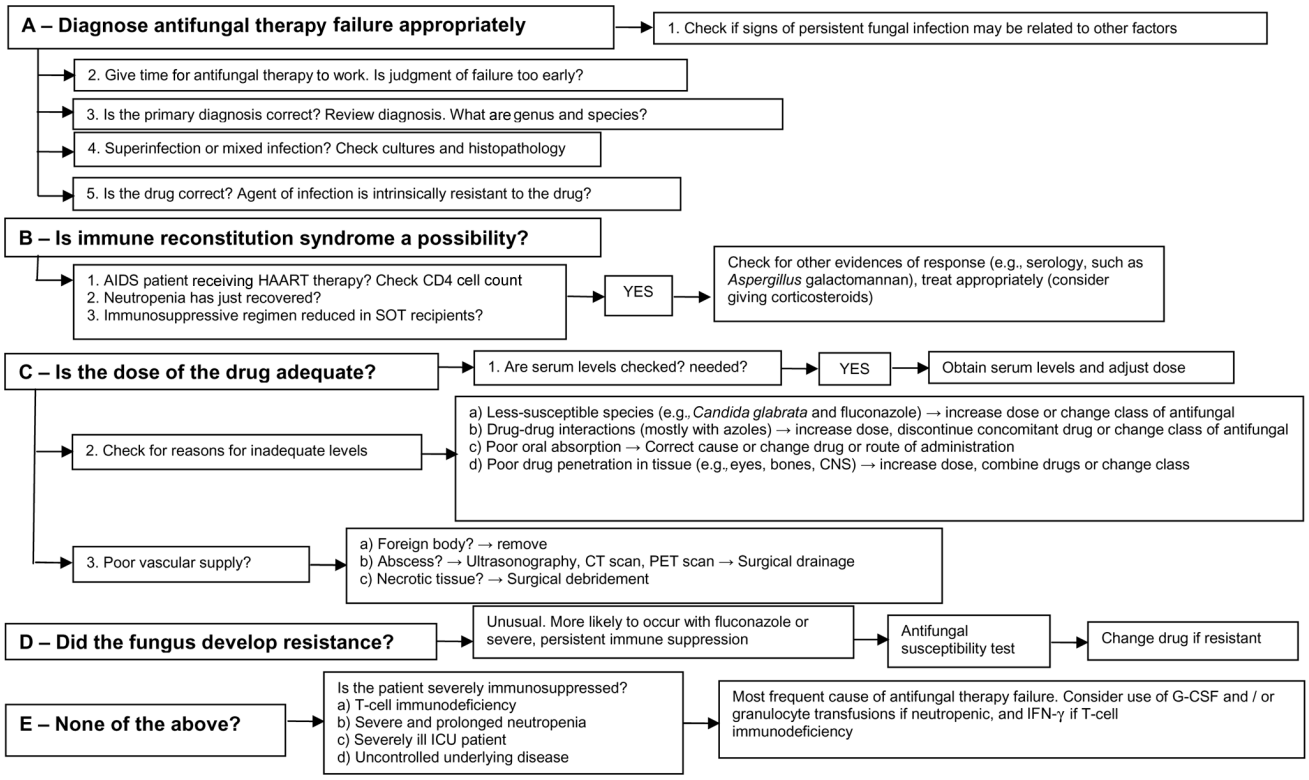

Figure 1. Approach to assessment of antifungal therapy failure. G-CSF, granulocyte colony–stimulating factor; ICU, intensive care unit; PET, positron emission tomography; SOT, solid organ transplant.

a precise definitio of antifungal therapy failure is, at times, difficult Because clinical signs and symptoms of an IFI can be nonspecific the use of these clinical parameters to characterize treatment failure may lead to erroneous interpretations. For example, persistent fever and hypotension despite antifungal treatment in a candidemic patient admitted to an intensive care unit is not necessarily synonymous with treatment failure, because these manifestations may also be attributable to other factors, such as concomitant infections, underlying medical conditions, and comorbidities. In other contexts, the presence of immune reconstitution inflammato y syndrome (IRIS) may result in an exacerbation of inflammato y manifestations of infection and the erroneous interpretation of drug failure [17]. The task becomes easier when the diagnosis is based on a positive culture result and results of additional cultures remain positive. However, because of the general poor sensitivity of cultures in the diagnosis of IFIs, negative culture results do not necessarily mean that the patient is responding to treatment; conversely, the preciseness of when persistent positive culture results defin failure is not always clear. In addition, in some patients with tissue involvement, it may be difficul to obtain additional samples for culture or histopathologic examination. In some instances, serological tests may help in evaluating clinical response. This is the case with the polysaccharide antigen test for histoplasmosis [18]. In addition, recent data suggest that persistently high serum galactomannan titers may correlate with therapy failure in IA [19, 20]. Another problem that complicates the diagnosis of treatment failure is that there are no definition of the minimum duration of treatment that clinicians should wait to assess therapeutic response. Surely, the response to therapy for candidemia is expected to be quicker than that for IA.

The most organized concepts of success and failure of antifungal therapy are obtained in the randomized clinical trials of antifungal drugs or in studies of salvage therapy. However, even in these studies, different criteria are used, especially in the timing of the end-point evaluation for success. For example, in the majority of studies of candidemia, although success was define as clinical and microbiological response, the end-point assessment varied, leading to different success rates among the studies [4, 6, 8, 10, 11].

Figure 1 presents a list of questions that may help to approach assessment of antifungal therapy failure. From this list, we can suggest a definitio of antifungal therapy failure as a diagnosis of exclusion, as follows: (1) persistence of clinical manifestations of infection at an appropriate time for a given infection (e.g., 2 weeks for candidemia and 6 weeks for IA), (2) primary diagnosis confi med, (3) superinfection or mixed infection

ruled out, (4) dosage and choice of antifungal drug correct, (5) poor vascular supply ruled out (e.g., abscess, foreign body, and necrotic tissue), and (6) IRIS ruled out.

FREQUENCY OF THERAPY FAILURE

With the limitations in the definition of antifungal therapy failure, it is difficul to assess its frequency. For example, for the candidemia trials mentioned above, the reported rate of failure had a range of 20%–30% when success was evaluated at the end of treatment [10], 30%–40% after intravenous therapy [6], 30%–45% with time-to-success analysis [11], 40%–50% at day 7 of therapy [8], and 60% when clinical response was assessed after 12 weeks of treatment [4]. In IA, the overall 12-week failure rate of patient treatment with voriconazole was 47.2% but was 68% among allogeneic hematopoietic stem cell transplant recipients [13]. In the fina end-point evaluations for treatment failure, substantial differences in certain risk groups reflec the strong impact of host defenses and/or underlying disease on the prognosis.

Table 1. Causes of antifungal therapy failure.

Causes of antifungal therapy failure
Host factor
Severity of illness
Persistence of immunodeficiency (e.g., neutropenia or use of corticosteroids)
Primary (intrinsic) drug resistance
Wrong diagnosis
Mixed infection
Low concentration of the drug at the site of infection
Pharmacokinetic and pharmacodynamic
Drug interactions
Biofilms
Poor vascular supply (e.g., abscess and necrotic tissue)
Drug toxicities (direct and with drug interactions)
Development of resistance (secondary)
Misdiagnosis of failure—immune reconstitution inflammatory syndrome

DIFFERENTIAL DIAGNOSIS OF TREATMENT FAILURE

The host. Host factors are the strongest prognostic factors for IFI and are the most frequent cause of therapy failure (table 1). These factors reflec either the general health of the patient influence by the underlying disease and its comorbidities (severity-of-illness scores) or the net state of immunosuppression. In candidemia, different severity-of-illness scores have been shown to be independent predictors of poor outcome [11, 21–27]. In patients with hematologic malignancies, persistent neutropenia is a predictor of poor outcome in different IFIs [16, 21, 25, 28], and in hematopoietic stem cell transplant recipients, surrogate markers of severe immunosuppression (e.g., receipt of corticosteroids, graft-versus-host disease, and monocytopenia) are important prognostic factors [29, 30].

By contrast, immune recovery is frequently associated with treatment success, and an example is the ability for HAART to improve the outcome of IFIs without the use of secondary suppressive antifungal treatment [31, 32]. These are clear-cut examples in which failure of treatment is controlled by recovering host immunity. However, what is less certain is how we can effectively use recombinant immune modulators—such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, granulocyte transfusions, and IFN-γ—to prevent antifungal therapy failure. There is no strong evidence-based clinical data to prove the value of immune modulators in established IFIs.

At the opposite side of immunosuppression is IRIS. During an IFI, the changing immune system may overshoot its protective behavior and actually add to disease. IRIS is well characterized during HAART administration in patients with AIDS who have IFIs [33], in solid organ transplant recipients with cryptococcosis [34], and in neutropenic patients with rapid neutrophil recovery during management of pulmonary IA [35, 36]. In any situations in which an IFI is being treated and immunity is rapidly changing (e.g., monoclonal antibodies and postpartum), IRIS has the potential to complicate treatment management. With the recurrence of inflammato y signs and symptoms, it either causes the perception of treatment failure or at least confuses the interpretation of successful management. For the clinician, it is necessary to ensure that symptoms and signs are not associated with persistent infection with viable fungal species because of culture results and/or biomarkers, to interpret the clinical presentation and timing, and to consider IRIS, because no specifi test is sufficien to correctly diagnose IRIS. Recognition of IRIS might allow a patient to not be categorized as experiencing antifungal therapy failure; in severe cases, the administration of an immunosuppressive or anti-inflammato y agent, such as a corticosteroid, may be necessary.

The fungus. Another important cause of treatment failure is the possibility that the fungal species causing disease is intrinsically resistant to the antifungal drug used in the treatment. Examples of intrinsically resistant fungal species include *Candida krusei* (resistant to fluconazole [37], *Scedosporium apiospermum* (resistant to amphotericin B) [38], *Aspergillus terreus* (resistant to amphotericin B) [39], and zygomycetes (resistant to voriconazole) [40]. With the advent of emerging fungal species, the list of mycoses with primary drug resistance appears to be enlarging (from *Scedosporium prolifican* to *Aspergillus lentulus* [41, 42]). An expert laboratory is critical for the proper identificatio of strains and, in selected cases, for performing in vitro susceptibility testing for unusual isolates or isolates affecting patients who experience infection relapse. Although

Table 2. Drugs that significantly decrease the serum levels of antifungal agents.

Antifungal agent	Concomitant drug(s)	Action
Itraconazole		
In capsules	H-2 antagonists and proton pump inhibitors	Monitor itraconazole serum levels
Capsule or oral solution	Rifampin	Consider increasing the dose of itraconazole or choosing alternate drug(s)
Fluconazole	Rifampin	Consider increasing the dose of fluconazole
Voriconazole	Rifampin, rifabutin, efavirenz, ritonavir, carbamazepine, long-acting barbiturates, and phenytoin	Contraindicated coadministration with carbamazepine, long-acting barbiturates, rifampin, and rifabutin; with phenytoin and efavirenz, double voriconazole dosage and monitor for increased levels of the concomitant drug
Posaconazole	Cimetidine, rifabutin, and phenytoin	Avoid concomitant use
Caspofungin	Rifampin, efavirenz, nevirapine, dexamethasone, phenytoin, and carbamazepine	Increase maintenance dose of caspofungin to 70 mg/day

accurate breakpoints are still uncertain except for some yeasts and antifungals, in vitro susceptibility results can be used to appreciate the potential of an antifungal drug's success in treatment.

Failure may also be attributable to the development of drug resistance while a patient is receiving antifungal agents. This has best been chronicled in mucosal candidiasis in patients with AIDS who are treated with azoles [43]. However, outside this context, the rates of resistance among *Candida* isolates causing systemic infection are far less frequent. For example, among 2000 *Candida* bloodstream isolates from 2 trials, the overall rate of resistance to fluconazol was only 6% [44]. The potential importance of antifungal drug resistance as a cause of antifungal therapy failure is further limited by the fact that a good correlation between MICs and clinical outcome has not been clearly established, with the exception of the azoles for candidiasis. With the echinocandins, no correlation between MIC and outcome was observed among 515 *Candida* isolates obtained from patients with esophageal candidiasis and among 231 isolates obtained from patients with invasive candidiasis [45]. Likewise, no correlation was observed between MIC values of different drugs and the outcome for 74 patients with cryptococcosis [46]. With molds, attempts to establish breakpoints have not been successful [47]. Nevertheless, despite these limitations, there are reports of infection due to isolates that develop resistance after exposure to antifungal drugs. The most frequent association is previous use of azoles and infection due to *Candida glabrata* [48, 49]. In addition, there are some reports of an increase in MIC values of isolates of *Candida* species to the echinocandins in patients receiving caspofungin [50–52] and of *Aspergillus* species that develop multiazole resistance after prolonged exposure to azoles [53]. However, systematic susceptibility tests of sequential isolates of *Aspergillus fumigatus* recovered from treated patients suggest that the development of direct resistance during treatment with amphotericin B is uncommon [54]. With regard to *Cryptococcus neoformans,* a recent study showed that 16 (76%) of 21 relapses of culture-positive relapses of cryptococcal meningitis treated with flu conazole were caused by isolates with reduced susceptibility to fluconazol [55] but may have been associated with the widespread exposure to azoles in a severely immunosuppressed population.

Access of the drug to the site of infection. Another reason for failure of antifungal treatment is infection occurring at a body site known to be difficul for fungal eradication, such as certain endovascular infections (e.g., endocarditis, septic thrombophlebitis, osteomyelitis, and endophthalmitis), infection in the CNS, certain deep-tissue abscesses, and infection associated with prosthetic material, with the formation of biofilms. The common feature of most of these infections is a low concentration of the drug at the site of infection, because of pharmacokinetic and/or pharmacodynamic characteristics of the drug (for CNS infections, endophthalmitis, and osteomyelitis), formation of biofilm (for endocarditis, thrombophlebitis, and infection on prosthetic material), or poor vascular supply (for abscess and necrotic tissue). In most instances, a combination of these factors is present, which can amplify the difficultie in successfully clearing an infection and may be major reasons for failure of treatment with a primary antifungal drug.

Candida species (and other microorganisms) within biofilm have high MICs against most antifungal drugs [56], although echinocandins and lipid polyenes appear to possess more activity against biofil yeasts than do azoles [56]. Treatment of infections associated with medical devices frequently fails with antifungal therapy alone and generally requires removal of the device [57]. For this reason, when primary antifungal therapy is failing, the clinician should consider every medical device used in patient care to be the potential cause of treatment failure until proven otherwise.

Drug kinetics. Low concentrations of the drug at the site of infection may be caused by fast drug metabolism [58], drug-

Table 3. Therapy management issues for failure of treatment with specific fungal infections.

Therapy management issues for treatment failure
Cryptococcal meningitis
Acute and chronic intracranial pressure problems can cause treatment failure
Most persistently positive CSF culture results occur because of less aggressive induction therapy
Treat with 2–3 weeks of induction therapy with polyene and flucytosine
Consider microbiological failure if positive CSF culture results at 8–10 weeks of initial therapy
If culture results are still positive, test for azole susceptibility and restart with combination antifungal induction therapy
Define agent for clearance phase on the basis of susceptibility
Consider IFN-γ if culture results are persistently positive after repeated induction therapy
Consider immune reconstitution inflammatory syndrome; cryptococcal antigen or nonviable yeasts in CSF are not necessarily biomarkers for eventual microbial failure
Candidemia
If persistent candidemia, consider removal and/or change catheters and drain abscesses
Compare initial and persistent isolates for in vitro susceptibility to azoles and candins
Identify *Candida* to species level, to predict drug susceptibility and natural history of infection
Change classes of antifungals (candins, azoles, or polyenes) with retreatment
Invasive aspergillosis
Identify fungal isolate to species level; attention to drug-resistant strains, such as *Aspergillus ustus*, *Aspergillus terreus,* and *Aspergillus lentulus* [42, 77]
Check azole, polyene, and candin in vitro susceptibility
Check the diagnosis
Check antifungal drug level in serum (azoles)
Consider surgical removal of a large necrotic focus
Consider combination therapy or change in individual class of antifungal for retreatment

drug interactions that reduce oral absorption or increase drug metabolism [59], or simply an inadequate dose for the size of the patient, and/or organ dysfunction(s) [60, 61]. With regard to the antifungal dose, the usual fluconazol dose of 400 mg/day for the treatment of invasive candidiasis may be inadequate if the infection is caused by certain strains of *C. glabrata* [62]. Alternatively, there are no precise recommendations for the adequate dose of amphotericin B. For example, a recent study comparing 3 mg/kg/day with 10 mg/kg/day of liposomal amphotericin B for the treatment of IA surprisingly failed to show superiority for the high-dose arm [12]. Nevertheless, in most instances, clinicians increase the dose of a lipid formulation of amphotericin B when the patient is not responding to initial treatment doses. With regard to the echinocandins, a study of candidemia did not show differences in response rates between 2 doses of micafungin (100 mg/day and 150 mg/day) and 1 dose of caspofungin (50 mg/day) [7]. Interestingly, some isolates of *Candida albicans* exhibit a paradoxical growth in vitro and in vivo when exposed to high concentrations of caspofungin [63]. The clinical significanc of these in vitro observations is not clear. Therefore, few data remain that support the increase in the dose of an antifungal drug to very high levels as a strategy to improve the outcome after initial failure of therapy for IFIs, despite the widespread acceptance of this strategy. On the other hand, in children, it is more likely that antifungal therapy failure is caused by an inadequate dose, because, in general, the clearance of these drugs in children is higher than in adults, and the optimal dose of many antifungal agents in children is not well established [60] and is probably insufficien with use of adult guidelines.

Table 2 shows a list of the drug interactions that may significantl reduce serum concentration of antifungal drugs, as well as the recommended actions for each situation. Most of the drug-drug interactions occur with the azoles [59, 64–67], and interactions that may compromise the treatment of the IFI rarely involve the other classes of antifungal drugs, with the exception of caspofungin [68].

Another important area for antifungal drug failure is organ toxicity. This factor may take the form of drug interactions in which an azole may increase levels of tacrolimus or cyclosporine to direct toxic levels in the kidney or hematopoietic system. On the other hand, the antifungal drugs may have direct toxicity on host organs; the most significan example is renal failure associated with amphotericin B [69].

Wrong diagnosis or mixed infection. A critical factor that should be checked when the patient is not responding to treatment is whether there was simply a wrong diagnosis. Some IFIs have similar clinical presentations and appearances in tissue. A typical example is zygomycosis in neutropenic patients, with its clinical picture similar to that of IA, with pulmonary nodules and a halo sign [70]. In this context, if voriconazole is started empirically on the basis of a halo sign and persistent neutro-

penia, the patient's condition will not improve. The same clinical scenario is true for a tissue diagnosis of a hyalohyphomycosis caused by a resistant strain. Therefore, lack of response to primary treatment must prompt the physician to reevaluate the diagnosis and to confi m the identificatio of the fungus. This might require PCR-based techniques in histopathological specimens if culture specimens are not available or fail to grow [71].

Finally, antifungal therapy failure may be caused by mixed infection. Not infrequently, the severely immunosuppressed patient has a combination of bacterial and fungal infections [72], viral and fungal infections [73, 74], or even infection caused by 2 different fungal pathogens [75]. In this context, treating only 1 infection may give an impression of failure of the antifungal drug regimen.

MANAGEMENT OF ANTIFUNGAL THERAPY FAILURE

The management of antifungal treatment failure is paradoxically both simple and complex (figu e 1). The simple part is to ask a series of questions. Is the patient's therapy really failing? Do we have biomarker, radiograph, culture, and/or histopathologic proof of failure? Is there too little immunity or too much? What is clinically happening with the underlying disease? Do we have in vitro susceptibility test results? Do we know the natural course of infection with the identifie fungal species? Have there been any antifungal drug administration issues or concerns (i.e., pharmacokinetics, toxicity, drug-drug interactions, and/or site of infection)? Have we given the therapy an appropriate length of time before evaluating for failure?

There is no exact plan for the management of antifungal treatment failure. The condition is heterogeneous and individual dependent, but there are certain principles that are helpful to consider.

1. Most antifungal therapy failures are linked to poorly controlled underlying disease. An appraisal of the management of the underlying disease and its impact on the IFI is essential.
2. Clinicians must make an effort to demonstrate evidence of failure to eliminate viable fungus from tissue or flui cultures, decreasing or elimination of fungal biomarkers, and/or histopathologic evidence demonstrating removal of fungal species from tissue.
3. There is a need for reassessment, with measurement of drug levels in the blood, of the antifungal drugs administered and a need for optimization of net immune status by either reducing the number of immunosuppressive drugs or adding immune modulators.
4. Surgical removal of infected foci is a "bedside" decision, but for the patient who experiences treatment failure, surgical removal of infected necrotic tissue might be necessary. In addition, removal of all foreign bodies at the site of infection is encouraged.
5. Dosing changes may be considered, or change to a new antifungal class of drugs may be in order. In addition, depending on the circumstances, the consideration of combination therapy can be entertained for salvage therapy, although robust studies supporting drug combination remain weak [76].

Therapeutic management issues for failure of treatment of several specifi fungal species are presented in table 3. These suggestions do not have the strength of guidelines and express, in most instances, our opinion.

DISCUSSION

Antifungal therapy failure is frequent in IFIs. The clinician frequently attributes therapy failure to specifi drug resistance and then changes therapy or adds another antifungal drug to the regimen. However, direct resistance is uncommon, and other factors related to the host's underlying disease and/or immune status and drug pharmacokinetics and pharmacodynamics may play a greater role in antifungal therapy failure. Identificatio of the most likely reasons for failure is a difficul task but is critical for improvement of the outcome.

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