New Agents for the Treatment of Fungal Infections: Clinical Efficacy and Gaps in Coverage

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The incidence of fungal infections has increased globally, and the introduction of the newer triazoles and echinocandin antifungals is a more-than-welcome and long overdue development. In this report, we review the clinical trials evaluating the therapeutic efficacy of these new antifungal agents and examine possible gaps in coverage. Voriconazole has become the primary treatment for most forms of invasive aspergillosis in a number of centers, posaconazole offers a broad antifungal spectrum, and echinocandins are fungicidal against most Candida species. Moreover, the new agents are active against some fungi that are resistant to amphotericin B, may have a role in the management of fever and neutropenia, and provide exciting options for combination antifungal therapy. However, significant questions remain, including the management of breakthrough infections and treatment failures and the efficacy of the new antifungal agents against less common fungi.

The incidence of fungal infection is increasing. Amphotericin B was essentially the only available drug for treating systemic mycoses until the late 1980s. At that time, liposomal formulations of amphotericin B, fluconazole, and itraconazole became available. Within the past few years, new extended-spectrum triazoles (voriconazole and posaconazole) and echinocandin antifungals (caspofungin, micafungin, and anidulafungin) have been evaluated clinically.

This report will summarize the studies evaluating new antifungal agents that are approved by the US Food and Drug Administration (voriconazole, caspofungin, micafungin, and anidulafungin) or that have completed phase 3 clinical trials (posaconazole). We focus on the information obtained from published clinical trials that evaluate the use of these new agents in the treatment of adult patients.

INVASIVE CANDIDIASIS AND CANDIDEMIA

Caspofungin is better-tolerated and as effective as amphotericin B in treating invasive candidiasis (table 1). In a prospective, randomized, double-blind study that included 224 patients with candidemia or other invasive candidiasis, there were significantly fewer drug-related adverse events in the caspofungin group, and caspofungin was as effective as the comparator (success rate, 73.4% vs. 61.7%; 95% CI, −0.7% to 26.0%) [1]. Among the patients with candidemia, caspofungin was again as effective as deoxycholate amphotericin B, with a favorable response of 71.7% for the caspofungin group and 62.8% for the deoxycholate amphotericin B group [1]. Other echinocandin antifungals are less well studied for the management of invasive candidiasis [2, 4] (table 1). Of note, development of resistance during prolonged treatment with caspofungin can occur.

Guidelines suggest that, for patients with invasive candidiasis, physicians can use caspofungin, fluconazole, an amphotericin B preparation, or combination therapy with fluconazole plus amphotericin B [8]. The choice depends upon previous exposure to antifungals, incidence of fluconazole-resistant non-Candida albicans strains, the presence of comorbid conditions (such as renal failure), and the clinical status of the patient [8]. Recent clinical studies, including studies published after the guidelines became available (table 1), support this approach. However, on the basis of their efficacy against fluconazole-resistant Candida species, we consider caspofungin and amphotericin B primary therapies among neutropenic and critically ill patients. A cost-efficacy study is needed to determine whether the lower incidence of drug-related side effects associated with caspofungin make echinocandin a cost-effective choice, compared with the less expensive (but more toxic) amphotericin B.
Table 1. Clinical trials investigating the efficacy of newer antifungals for patients with invasive candidiasis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of subjects</th>
<th>Primary antifungal</th>
<th>Duration (mean, median)</th>
<th>Comparator</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mora-Duarte et al. [1]</td>
<td>Prospective, randomized</td>
<td>224</td>
<td>Cas, 70 mg iv loading dose, then 50 mg/day iv</td>
<td>1–28 days (12.1 days; 11 days)</td>
<td>AmB, 0.6–1 mg/kg per day iv for 1–28 days (11.7 days; 10 days)</td>
<td>Clinical response rate, 73.4% (Cas) vs. 61.7% (AmB) CI: 0.7–26.0; after adjustment for neutropenic status and the APACHE II score, the difference in the proportion of patients with a favorable response was 12.7% (95.6% CI: −0.7 to 26.0; P = .09)</td>
<td>There were significantly fewer drug-related adverse events in the Cas group than in the AmB group; laboratory abnormalities occurred in 24.3% vs. 54.0% of subjects (P = .002); withdrawal of therapy because of adverse effect occurred in 2.6% vs. 23.2% (P = .008); nephrotoxicity occurred in 8.4% vs. 24.8% (P = .02).</td>
</tr>
<tr>
<td>Ostrosky-Zeichner et al. [2]</td>
<td>Multicenter, open-label</td>
<td>126</td>
<td>Mica, 50–200 mg per day iv (adults)</td>
<td>5–42 days</td>
<td>None</td>
<td>Clinical response rate, 84.5%; patients who received 75–150 mg/day had higher success rates</td>
<td>Best results with Candida glabrata infection; study included 20 pediatric patients; 29 patients also received other antifungals</td>
</tr>
<tr>
<td>Kohno et al. [3]</td>
<td>Multicenter, open-label, dose comparison</td>
<td>7</td>
<td>Mica, 25–75 mg per day iv</td>
<td>7–29 days (16 days)</td>
<td>None</td>
<td>Clinical response rate, 85.7%</td>
<td></td>
</tr>
<tr>
<td>Krause et al. [4]</td>
<td>Open-label, dose ranging</td>
<td>83</td>
<td>Ani, 50 mg, 75 mg, or 100 mg per day iv</td>
<td>14–42 days</td>
<td>None</td>
<td>Clinical response rate for patients receiving Ani at 50 mg, 75 mg, and 100 mg per day was 84%, 90%, and 89%, respectively; at follow-up 2 weeks later, success rates were 72%, 85%, and 83%, respectively</td>
<td>Population with complicated comorbid conditions. No statistical significance between different doses, however trend toward higher success rates in the groups of 100 and 150 mg, compared to the 50 mg group.</td>
</tr>
<tr>
<td>Kullberg et al. [5]</td>
<td>Multicenter, randomized</td>
<td>370</td>
<td>Vori, 6 mg/kg twice daily iv (loading dosage), 3 mg/kg 2 times daily iv (maintenance dosage); after 3 days, patient can switch to 200 mg twice daily po</td>
<td>8 weeks</td>
<td>AmB, 0.7–1 mg/kg per day iv for 3–7 days, then Flu, 400 mg per day</td>
<td>Successful outcome in 41% of patients in both arms.</td>
<td>Vori as effective as AmB followed by Flu; Vori was more effective against Candida tropicalis (32% vs. 6% success rate) (P = .032)</td>
</tr>
<tr>
<td>Ostrosky-Zeichner et al. [6]</td>
<td>Salvage</td>
<td>52</td>
<td>Vori, 4–20 mg/kg per day</td>
<td>None</td>
<td>None</td>
<td>Clinical response rate, 56% overall, 44% for patients with C. albicans infection, and 70% for patients with Candida krusei infection</td>
<td></td>
</tr>
<tr>
<td>Perfect et al. [7]</td>
<td>Salvage</td>
<td>49</td>
<td>Vori, 6 mg/kg 2 times daily iv on day 1 (loading dosage), 4 mg/kg 2 times daily iv (maintenance dosage); after 3 days, patient can switch to 200 mg 2 times daily po</td>
<td>For iv therapy, 1–138 days (median duration, 18 days); for po therapy, 1–326 days (median duration, 69 days)</td>
<td>None</td>
<td>Clinical response rate, 55%</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. AmB, amphotericin B; Ani, anidulafungin; Cas, caspofungin; Flu, fluconazole; Mica, micafungin; Vori, voriconazole.
Of note is that patients who initially receive caspofungin, amphotericin B, or any other therapy can be switched to fluconazole as soon as affirmative susceptibility data or strain identification become available. This can be a cost-saving approach; however, there are some difficulties with this approach. In some clinical laboratories, susceptibility testing is not a routine procedure. Moreover, although voriconazole interpretable MIC breakpoints for *Candida* species were recently published by the Clinical and Laboratory Standards Institute (formerly the NCCLS), susceptibility breakpoint numbers for echinocandins are lacking. This approach also requires the change of antimicrobial therapy in a patient who is probably responding to the initial treatment, which is something that we are sometimes hesitant to do.

Regarding the role of the newer triazoles for the management of invasive candidiasis, voriconazole was as effective as a regimen of conventional amphotericin B followed by fluconazole for the treatment of candidemia in a large phase 3 clinical study that included 370 patients with candidemia [5]. Response to treatment was defined as mycological eradication and clinical cure or improvement. Importantly, neutropenic patients were excluded from this study, and patients in the amphotericin B and fluconazole group had a higher mean APACHE II score than patients in the voriconazole group. Response to treatment, defined as mycological eradication and clinical cure or improvement at the 12-week follow-up visit, was the primary end point; the rate of response to treatment was 41% in both study groups. The mortality rate was also similar between the 2 groups; 88 (36%) of 248 patients in the voriconazole group and 51 (42%) of 122 patients in the amphotericin B and fluconazole arm died (P = .23). Voriconazole was better tolerated, and among patients infected with *Candida tropicalis*, voriconazole administration resulted in a significantly higher treatment success rate, compared with amphotericin B and fluconazole; 17 (32%) of 53 patients in the voriconazole group had treatment success, compared with 1 (6%) of 16 patients in the amphotericin B and fluconazole group (P = .023).

A clinical study comparing the efficacy of voriconazole with that of echinocandins would help to define the role of voriconazole in the management of invasive candidiasis in general and as an alternative in the treatment of infections due to *Candida* species, such as *Candida guilliermondii* and *Candida parapsilosis*, that may be less susceptible to echinocandins. The efficacy of voriconazole against *C. tropicalis* is also intriguing and deserves further study. Notably, *Candida lusitaniae* isolates are often resistant to amphotericin B. Fluconazole is the preferred therapy for this species, and echinocandins and voriconazole can provide additional alternatives, but this requires further validation in clinical trials.

**ESOPHAGEAL CANDIDIASIS**

Fluconazole, which is now off patent, remains primary therapy for most cases of esophageal candidiasis (or oropharyngeal candidiasis requiring systemic therapy), whereas voriconazole, caspofungin, and probably micafungin are effective in the management of fluconazole-refractory cases, including infections due to *Candida glabrata* and *Candida krusei* (table 2). More specifically, caspofungin is effective in the treatment of *Candida* esophagitis [11, 17], and response and relapse rate are similar to those associated with fluconazole [11] and deoxycholate amphotericin B [9, 10]. Micafungin is also as effective as fluconazole [3, 12–14], but clinical experience with micafungin is less than that with caspofungin. Anidulafungin is also as effective as fluconazole [15], but more studies are needed. Voriconazole, which is also equally as effective as fluconazole, is available for oral therapy and can be effective even against some fluconazole-refractory isolates [16]. Itraconazole solution is another option for treating esophageal candidiasis, including fluconazole-refractory cases, and intravenous amphotericin B formulations can also be used for treating patients with otherwise refractory disease [8]. Of note is that echinocandins can be given only intravenously, and their cost is significantly greater than that of fluconazole. In addition, echinocandins may demonstrate higher relapse rates, compared with fluconazole, although this difference has reached statistical significance only for anidulafungin [11, 12, 15] (table 2). Finally, adverse events related to voriconazole treatment were more frequent than adverse events related to fluconazole treatment [16].

**INVASIVE ASPERGILLOSIS**

In many centers voriconazole has become the drug of choice for the management of documented invasive aspergillosis (table 3). In a large clinical trial that included 277 patients with pulmonary disseminated aspergillosis, successful outcome was observed in 52.8% of patients who received voriconazole and in 31.6% of patients who received amphotericin B (95% CI, 10.4%–32.9%) [18]. Moreover, patients in the voriconazole group had a higher survival rate and fewer side effects than did patients in the amphotericin B group [18]. Similar results were found in a smaller, noncomparative study [19], as well as in a salvage therapy trial [7]. Preliminary data suggest that posaconazole is also active against *Aspergillus* species.

The efficacy of caspofungin for the management of invasive aspergillosis has been tested as salvage therapy in 2 studies [21, 22]. In the study by Kartsonis et al. [21], 45 patients were assessed; 9 (20%) of the patients showed complete response, and 11 (24%) showed partial response, with a greater response rate noted for patients with pulmonary aspergillosis than for patients with extrapulmonary aspergillosis (52.9% vs. 18.1%,
Table 2. Clinical trials investigating the efficacy of newer antifungals for patients with oropharyngeal or esophageal candidiasis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of subjects</th>
<th>Primary antifungal</th>
<th>Duration</th>
<th>Comparator</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villanueva et al. [9]</td>
<td>Multicenter, randomized, double-blind, dose comparison</td>
<td>128</td>
<td>Cas, 50 mg or 70 mg per day iv</td>
<td>14 days</td>
<td>AmB, 0.5 mg/kg iv</td>
<td>Endoscopically verified clinical success at 14 days after treatment in 74% (50 mg group) or 89% (70 mg group) in the Cas arm, compared with 63% in the AmB arm</td>
<td>Significantly lower incidence of drug-related clinical adverse events for each Cas study arm vs. amphotericin B arm (P &lt; .01)</td>
</tr>
<tr>
<td>Arathoon et al. [10]</td>
<td>Randomized, double-blind, dose comparison</td>
<td>140</td>
<td>Cas, 35, 50, or 70 mg / day iv</td>
<td>OP group: 7 days; ES group: 10–14 days</td>
<td>AmB, 0.5 mg/kg iv</td>
<td>Clinical response rate, 74% (Cas 35 mg group), 91% (Cas 50 mg group), 82% (Cas 70 mg group), and 63% (AmB group)</td>
<td>Significantly lower incidence of adverse events in the Cas groups (P &lt; .01)</td>
</tr>
<tr>
<td>Villanueva et al. [11]</td>
<td>Multicenter, randomized, double-blind</td>
<td>175</td>
<td>Cas, 50 mg per day iv</td>
<td>1–20 days (mean duration, 9.4 days)</td>
<td>Flu, 200 mg per day iv</td>
<td>Overall clinical response rate, 81% (Cas group) vs. 95% (AmB group); clinical response rate for patients with Candida glabrata 93% (Cas group) vs. 67% (AmB group)</td>
<td>Greater relapse rate for Cas group than AmB group (28% vs. 17%); not statistically significant</td>
</tr>
<tr>
<td>de Wet et al. [12]</td>
<td>Multicenter, randomized, double-blind</td>
<td>523</td>
<td>Mica, 150 mg per day iv</td>
<td>Median duration, 14 days</td>
<td>Flu, 200 mg per day iv</td>
<td>Endoscopic cure rate, 87.7% vs. 88%</td>
<td>Relapse rate, 15.2% vs. 11.3% (not statistically significant); rate of drug-related adverse events, 27.7% (Mica group) vs. 21.3% (Flu group) (not statistically significant)</td>
</tr>
<tr>
<td>Pettengell et al. [13]</td>
<td>Multicenter, open-label</td>
<td>84</td>
<td>Mica, 12.5–100 mg per day iv</td>
<td>14–21 days</td>
<td>None</td>
<td>Clinical response rate, 66.6%, 92.3%, 93.3%, and 100% for dosage groups of 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg per day, respectively</td>
<td>Mica significantly more active at doses &gt;50 mg per day</td>
</tr>
<tr>
<td>de Wet et al. [14]</td>
<td>Multicenter, randomized, double-blind, dose escalation</td>
<td>245</td>
<td>Mica, 50, 100, or 150 mg per day iv</td>
<td>14–21 days</td>
<td>Flu, 200 mg per day iv</td>
<td>Endoscopic cure rate, 68.8%, 77.4%, and 89.8% in the Mica arm vs. 86.7% in the Flu arm</td>
<td>Mica, 150 mg more effective than Mica, 50 mg, (P = .024); comparable success rate for Mica (at dosages of 100 and 150 mg per day) and Flu (P = .136 and P = .606, respectively)</td>
</tr>
<tr>
<td>Kohno et al. [3]</td>
<td>Multicenter, open-label</td>
<td>7</td>
<td>Mica, 25, 50, or 75 mg per day iv</td>
<td>7–29 days (mean duration, 16 days)</td>
<td>None</td>
<td>Clinical response rate overall, 71%; for 25-mg group, 0%; for 50-mg group, 100%; for 75-mg group, 100%</td>
<td>No successful outcomes with 25 mg per day iv</td>
</tr>
<tr>
<td>Krause et al. [15]</td>
<td>Multicenter, randomized, double-blind</td>
<td>494</td>
<td>Ani, 100 mg iv loading dose on day 1, then 50 mg per day iv</td>
<td>14–21 days</td>
<td>Flu, 200 mg loading dose on day 1, then 100 mg per day</td>
<td>Endoscopic success rate, 97.2% vs. 96.8%</td>
<td>Similar success rates, greater relapse rates for Ani group (P = .001)</td>
</tr>
<tr>
<td>Perfect et al. [7]</td>
<td>Salvage</td>
<td>38</td>
<td>Vori, 6 mg/kg 2 times daily iv (loading dosage), followed by 4 mg/kg 2 times daily iv for at least 3 days, then switched to 200 mg 2 times daily po, or Vori, 400 mg 2 times daily po (loading dosage), followed by 200 mg 2 times daily po</td>
<td>iv group, 1–138 days (median duration, 18 days); po group, 1–326 days (median duration, 69 days)</td>
<td>None</td>
<td>Clinical response rate, 60.5%</td>
<td>...</td>
</tr>
<tr>
<td>Ally et al. [16]</td>
<td>Multicenter, randomized, double-blind</td>
<td>256</td>
<td>Vori, 200 mg 2 times daily</td>
<td>2–6 weeks</td>
<td>Flu, 400 mg once daily po</td>
<td>Clinical response rate, 98.3% (Vori group) and 95.1% (Flu group)</td>
<td>Similar success rates</td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B; Ani, anidulafungin; Cas, caspofungin; ES, esophageal; Flu, fluconazole; Mica, micafungin; OP, oropharyngeal; Vori, voriconazole.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of subjects</th>
<th>Primary antifungal dosage</th>
<th>Duration</th>
<th>Comparator</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbrecht et al. [18]</td>
<td>Multicenter, randomized</td>
<td>277</td>
<td>Voriconazole 6 mg/kg iv</td>
<td>2–84 days median (77 days)</td>
<td>AmB, 1–1.5 mg/kg iv once daily for 1–84 days (median, 10 days)</td>
<td>Rate of successful outcome, 52.8% for Voriconazole group and 31.6% for AmB group; survival rate: 70.8% vs. 57.9%, respectively (95% CI, 40%–68%; P = .008); duration of treatment was much longer for the Voriconazole group.</td>
<td>Voriconazole had fewer adverse events (343 vs. 421; P = .008) and fewer severe adverse events (26 vs. 45; P = .008).</td>
</tr>
<tr>
<td>Denning et al. [19]</td>
<td>Multicenter, open-label, noncomparative, salvage</td>
<td>116</td>
<td>Voriconazole 6 mg/kg iv</td>
<td>54–290 days median (133 days)</td>
<td>None</td>
<td>Clinical response rate, 48% (only 14% of subjects had complete response).</td>
<td>14% of subjects had complete response.</td>
</tr>
<tr>
<td>Perfect et al. [7]</td>
<td>Salvage</td>
<td>142</td>
<td>Voriconazole 6 mg/kg iv</td>
<td>1–138 days median (66 days)</td>
<td>None</td>
<td>Clinical response rate, 44%</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B; Voriconazole (Vori).
studies suggest that posaconazole may be useful in the treat-
agement of cryptococcosis is limited [7, 25]. In vivo and animal
Clinical experience with the new antifungal agents in the man-
vasive aspergillosis was poor [24].

Combination therapy for invasive aspergillosis with triazoles
and echinocandins holds promise because of their differing
mechanism of action. Antifungal triazoles exhibit their activity
by inhibiting the fungal lanosterol 14α-demethylase, an enzyme
that catalyzes a key step in ergosterol biosynthesis and, although
the full extent of echinocandin antifungal activity is under
study, it appears that they mainly act as a noncompetitive in-
hibitor of (1,3)β-glucan synthase, a key enzyme in fungal cell
wall synthesis. Marr et al. [23] performed a retrospective eval-
uation of the outcome for patients with proven or probable
invasive aspergillosis who received either voriconazole (31 pa-
tients) or a combination of voriconazole and caspofungin (16
patients) for salvage therapy. In a multivariable analysis, salvage
therapy with the combination of caspofungin and voriconazole
was associated with statistically significant improvement in the
3-month survival rate, compared with therapy with voricon-
aazole. Prospective, randomized trials are warranted to evaluate
the combination of voriconazole and caspofungin as primary
therapy for invasive aspergillosis. The combination of caspo-
fungin with liposomal amphotericin B has also been studied in
a retrospective study and was found to be relatively well
tolerated, but the response of patients with documented in-
vasive aspergillosis was poor [24].

CRYPTOCOCCOSIS

Clinical experience with the new antifungal agents in the man-
agement of cryptococcosis is limited [7, 25]. In vivo and animal
studies suggest that posaconazole may be useful in the treat-
ment of cryptococcal infections. Pitisuttithum et al. [25] eval-
uated the efficacy of posaconazole in therapy of patients with
CNS infection who had experienced the failure of previous
antifungal therapy. This study included 29 patients with cryp-
tococcal meningitis, and clinical response was noted for 14
(48%) of the 29 patients. The role, if any, of voriconazole in
the management of cryptococcosis is even less well studied, and
echinocandins have no clinical efficacy against Cryptococcus
neoformans.

LESS COMMON FUNGI

Clinical experience with the new antifungal agents against the
less common fungi is limited, at best. Voriconazole and echino-
candin antifungals are not active against Zygomycetes species
[26], and posaconazole demonstrates variable fungistatic activ-
ity against Zygomycetes species. A recent study [27] detailed the
results from the first 24 cases of patients with active zygo-
micosis who were enrolled in 2 open-label, nonrandomized com-
passionate trials evaluating the efficacy of posaconazole. The
pathogenic fungus was identified in 17 of 24 patients, and
clinical success rates with posaconazole therapy were 5 of 6
patients with infection due to Mucor species, 1 of 2 patients
with infection due to Rhizomucor species, 5 of 6 patients with
infection due to Rhizopus species, and 1 of 3 patients with
infection due to Cunninghamamella species [27]. Pending further
studies, we consider posaconazole to be an option for patients
that experience treatment failure with or cannot tolerate a full
dose of amphotericin B.

Voriconazole has efficacy against fusariosis, scedosporiosis,
and penicilliosis, and in a salvage therapy study, clinical re-
response to voriconazole was noted for 5 of 11 patients with
fusariosis, 3 of 19 patients with scedosporiosis, and 9 of 10
patients with penicilliosis [7]. However, amphotericin B appears
to be the primary treatment for infection due to Fusarium
oxysporum and Fusarium solani (as well as infection due to
Rhodotorula species). Posaconazole appears to have activity in
cases of fusariosis and scedosporiosis, as well as in cases of
chromoblastomycosis and phaeohyphomycosis. Dimorphic fungi
appear to be resistant to or less susceptible to echinocandins,
but most of these organisms are susceptible to the newer triazole
antifungals and are especially susceptible to posaconazole.
Other organisms that appear to be resistant to echinocandins
but that may be susceptible to the newer triazole antifungals include
Cladosiphialophora bantiana, Paeillomyces lilacinus, and
Trichosporon species. Some notable exceptions may be that
posaconazole seems to be less active against Sporothrix schenckii,
whereas micafungin may have some activity against dimorphic
fungi, C. bantiana, and P. lilacinus, but clinical data are lacking.

The efficacy of the new antifungals against less common
fungi needs to be studied in more detail, because it is important
not only for the treatment of patients who present with these
infections but also because lack of efficacy can translate into breakthrough infections or treatment failures during therapy. For example, Imhof et al. [26] retrospectively analyzed the clinical records of 139 patients who were treated with voriconazole. Breakthrough fungal infections occurred in 13 of 139 patients who received voriconazole, and Zygomycetes species were found in 6 of these 13 patients. Also, the use of combination therapy may have a role for the management of less common infections and should be studied.

EMPIRIC THERAPY IN FEVER AND NEUTROPENIA

Caspofungin and voriconazole have been evaluated as empiric therapies for patients with fever and neutropenia [18, 28, 29–32]. The efficacy of caspofungin for management of fever and neutropenia was evaluated in a group of 1095 patients (556 patients receiving caspofungin and 539 patients receiving liposomal amphotericin B). The overall success rates were 33.9% for patients receiving caspofungin and 33.7% for patients receiving liposomal amphotericin B (95.2% CI for the difference, −5.6% to 6.0%), fulfilling statistical criteria for the noninferiority of caspofungin therapy. Premature discontinuation of therapy occurred less often in the caspofungin group than in the amphotericin B group (10.3% vs. 14.5%; P = .03), and the rates of resolution of fever during neutropenia were similar in the 2 groups [29]. Caspofungin was also effective in a retrospective study that included 31 patients who underwent allogeneic stem cell transplantation; however, only 8 patients with proven fungal infection were included in this study [32].

A very interesting study evaluated the efficacy of voriconazole in the therapy of fever and neutropenia [28], and the data from this study, along with additional information provided by the manufacturer, were recently reviewed [30]. In this study [28], which did not include patients with liver failure, the number of patients discontinuing therapy because of toxic effects was similar in the voriconazole arm and the liposomal amphotericin B, whereas the number of patients discontinuing therapy because of a lack of efficacy was significantly different in favor of liposomal amphotericin B [28, 30]. The 95% CI for the difference exceeded the predefined limit for noninferiority of −10.0% [28, 30], and the Antiviral Drug Products Advisory Committee of the US Food and Drug Administration voted against accepting empirical use of voriconazole in patients with neutropenia as an indication for this drug [30, 31]. Voriconazole was also compared with deoxycholate amphotericin B [18]. Deoxycholate amphotericin B therapy performed significantly worse than voriconazole therapy. Notably, by design, this study did not include premedication or meticulous substitution with electrolytes [18, 30]. Also, posaconazole therapy was evaluated in a multicenter, open-label, parallel group study that included 66 patients with persistent febrile neutropenia. Overall clinical response was 74%–81%, depending on the dosage [33].

Taken in their totality, these data suggest that, for the antifungal management of fever and neutropenia, “one size fits all” no more. Liposomal amphotericin B provides adequate coverage for invasive aspergillosis and broad antifungal coverage that includes important infections in this population, such as invasive zygomycosis, and we consider it to be primary therapy for antifungal coverage in most patients with fever and neutropenia. Pending further studies, we reserve caspofungin therapy for patients at low risk for infection with a filamentous fungus (either as a primary infection or as a coinfection). For example, this includes some patients with heavy gastrointestinal colonization by Candida species and extensive mucositis because of chemotherapy.

Studies in populations with a high incidence of infection due to Aspergillus species may identify patients who can benefit from empirical voriconazole therapy for fever and neutropenia. Because new diagnostic techniques are becoming available, voriconazole, in particular, may have a role in the treatment of patients with fever and neutropenia who have peripheral blood laboratory test results positive for aspergillosis or of patients with a history of invasive aspergillosis who are undergoing subsequent immunosuppression. However, studies are needed to validate these approaches. Also, as noted above, there is a clear need for studies that evaluate the management of treatment failures associated with empiric use of the newer antifungal agents.

PRACTICAL CONSIDERATIONS

Gaps in coverage do not result only from limitations in the efficacy of the antifungal agent but are also the result of the antifungal agent’s safety profile. Triazoles and echinocandins have some interesting differences in contraindications and drug-drug interactions that need to be considered when deciding on antifungal therapy.

Contraindications and precautions. Voriconazole should be avoided for patients with severe hepatic insufficiency, and dosage adjustment is required for voriconazole therapy for patients with impaired hepatic function. Caspofungin does not require dosage adjustment in patients with mild hepatic insufficiency, although patients with moderate hepatic insufficiency (i.e., those with a Child Puch score of 7–9) should receive a decreased dose. No dosage adjustment is required for any of the echinocandins or for posaconazole in treating patients with renal failure. However, because intravenous formulations of voriconazole contain excipient sulfobutyl ether β-cyclodextrin, which may accumulate in patients with renal insufficiency, this formulation should be avoided for patients with moderate-to-severe renal failure.

Voriconazole tablets contain lactose, and oral therapy may
be associated with a higher incidence of adverse effects among patients with hereditary galactose intolerance, lactase deficiency, or glucose-galactose malabsorption. Voriconazole treatment can also affect vision by causing color changes, photophobia, blurred vision, or changes in visual acuity. Therefore, patients should be advised to avoid tasks that depend on vision, including operating machinery or driving. Caspofungin, micafungin, and voriconazole should be avoided during pregnancy, and they are designated category C (risk to the fetus cannot be ruled out), C, and D (positive evidence of human fetal risk), respectively. For comparison, formulations of amphotericin B are designated category B (no evidence of fetal risk), and fluconazole and itraconazole are also designated category C [34].

**Drug interactions.** Triazoles should be administered with caution to patients receiving medications that are metabolized by the cytochrome P450 isoenzymes. For example, coadministration of voriconazole and phenytoin requires an increase of voriconazole dose and monitoring of drug levels for phenytoin and, possibly, voriconazole. Drug levels should be monitored when triazoles are used together with sirolimus and cyclosporine (triazoles increase plasma concentrations of these drugs), and triazole can increase warfarin-induced prothrombin time. Triazoles should be used with caution when administered with some chemotherapeutic agents, such as vinca alkaloids and cyclophosphamide, and patients should be warned to avoid St. John’s wort.

Caspofungin may decrease the serum concentration of tacrolimus, and careful monitoring of the latter drug is needed. In addition, the manufacturer recommends maintaining dosages at 70 mg per day when caspofungin is coadministered with rifampin, because rifampin may decrease the serum concentration of caspofungin. Micafungin may increase nifedipine and sirolimus concentrations, although the clinical significance of these interactions appears to be minimal. Of interest, the bioavailability of voriconazole decreases with fatty meals, whereas the bioavailability of posaconazole increases with food.

Importantly, further studies evaluating drug levels of the new antifungal agents are needed. For example, voriconazole levels can vary considerably, and monitoring levels can be useful for selected patients who are receiving voriconazole for severe fungal infection, especially among those with abnormal liver function [35].

**CONCLUSIONS**

With the antifungal agents detailed above and additional agents that are in earlier stages of development, we are now able to provide to our patients individualized, more-effective, and less toxic antifungal therapy. Moreover, combinations of antifungals may provide even better choices against difficult-to-treat systemic fungal infections. Yet, “to whom much is expected” (Luke 12:48), and what is expected from us is to use these new antifungals following an evidence-based approach.

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