**Anidulafungin was noninferior to fluconazole for invasive candidiasis**


**Clinical impact ratings:** Hospitalists ★★★★★☆ Endocrinology ★★★★★☆ Infectious Disease ★★★★★☆ Critical Care ★★★★★☆ Nephrology ★★★☆☆☆☆ Oncology ★★★★★☆☆

**Question**
In patients with candidemia or other forms of invasive candidiasis, is anidulafungin non-inferior to fluconazole?

**Methods**
Design: Randomized, controlled, noninferiority trial.
Allocation: [Concealed]†.*
Blinding: Blinded.*
Setting: 47 institutions in 6 countries in Europe and North America.
Follow-up period: 6 weeks after completion of therapy.

**Patients:** 261 patients ≥ 16 years of age who had candidemia (≥ 1 positive blood culture) or other forms of invasive candidiasis (a positive culture obtained from a sterile site) within 96 hours of enrollment and ≥ 1 of fever, hypothermia, hypotension, local signs and symptoms, or radiologic findings of invasive candidiasis. Exclusion criteria were > 48 hours of systemic antifungal therapy, prophylactic administration of any azole for > 1 week within 30 days, refractory candida infection, elevated hepatic enzymes, *Candida krusei* infection, osteomyelitis, endocarditis, or meningitis due to *Candida* infection.

**Intervention:** Intravenous (IV) anidulafungin, 200 mg on day 1 and then 100 mg/d (n = 132), or IV fluconazole, 800 mg on day 1 and then 400 mg/d (n = 129), for 14 to 42 days and for ≥ 14 days after negative blood culture and improvement in signs and symptoms.

**Outcomes:** Global treatment response based on clinical success (resolution of signs and symptoms and no need for additional systemic antifungal therapy) and microbiologic success (eradication of *Candida* species present at baseline on follow-up culture or presumed eradication if no available culture and successful clinical response) at the end of IV therapy. Secondary outcomes included death and adverse events.

**Patient follow-up:** 94% (mean age 58 y, 51% men) were included in the modified intention-to-treat analysis (received ≥ 1 dose of study medication), and 98% were included in the intention-to-treat analysis.

**Main results**
Global response at the end of IV therapy was achieved in 76% of patients in the anidulafungin group and 60% in the fluconazole group (absolute difference 15%, 95% CI 4 to 27) (Table). This met the prespecified criteria for noninferiority (i.e., lower limit of CI > −20%) and for superiority (i.e., CI excluded 0). The groups did not differ for death or adverse events (Table).

**Conclusion**
In patients with candidemia or invasive candidiasis, anidulafungin was noninferior to fluconazole.

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*See Glossary.
†Information provided by author.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ANID</th>
<th>FLUC</th>
<th>RBI (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global response at the end of IV therapy</td>
<td>76%</td>
<td>60%</td>
<td>26% (6 to 51)</td>
<td>7 (4 to 27)</td>
</tr>
<tr>
<td>Death at 6 wk†</td>
<td>23%</td>
<td>31%</td>
<td>27% (−1 to 51)</td>
<td>Not significant</td>
</tr>
<tr>
<td>≥ 1 treatment-related adverse event at 6 wk</td>
<td>24%</td>
<td>26%</td>
<td>7% (−41 to 39)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

†Abbreviations defined in Glossary. RBI, RRR, NNT, and CI calculated from data in article.
‡Clinical and microbiological success. Based on modified intention-to-treat population (received ≥ 1 dose of study medication).
| Based on intention-to-treat analysis. |

The trial by Reboli and colleagues included mainly nonneutropenic patients with candidemia, appropriately excluded patients with a higher likelihood of fluconazole-resistant *Candida*, and assessed clinical and microbiological success at the end of IV therapy as primary endpoints. Multivariate analysis was done to account for possible sources of bias, including immunosuppression, diabetes, prior azole therapy, *C. glabrata* (less likely to respond to fluconazole), and catheter removal (the catheter remained in place in 4 patients in the anidulafungin group and 11 in the fluconazole group).

Typically, noninferiority trials can only establish that a new drug is not ‘so much’ worse than a standard treatment. The ‘so much’ is a percentage chosen mainly for statistical reasons: The smaller the difference, the larger the sample size required. In this case, the null hypothesis (which must be rejected to establish noninferiority) was that “anidulafungin is at least 20% worse than fluconazole.” The criterion of 20% is fairly standard and has been used in similar studies. In fact, the results of Reboli and colleagues favored anidulafungin over fluconazole (success rate 76% vs 60%). This is one of the few noninferiority trials in which the tested drug fulfilled the prespecified criteria for superiority: The 15% absolute difference in success rates had a 95% CI of 4 to 27, which excluded the prespecified criterion for superiority of 0.

The authors, as well as the editorialists (1), tiptoe around this fact, probably because the criteria to establish superiority in a noninferiority trial are not universally accepted and because at 6-week follow-up the criterion for superiority was no longer met (although the criterion for noninferiority was still met). Regardless, the study convincingly shows that anidulafungin is at least as effective as fluconazole for treating candidemia in nonneutropenic patients. Fluconazole, amphotericin, and echinocandins seem to have similar efficacy, and choosing one over another should be based on specific characteristics of the patient and institution.

**Reference**