

ALTERNATIVE VIEWPOINTS

Use of Echinocandins for *Candida parapsilosis* Infections

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Key Words: Echinocandins, *Candida parapsilosis*, Antifungals, Non-*albicans* *Candida*

(Pharmacotherapy 2011;31(3):87e–88e)

We commend the work by Kale-Pradhan and colleagues, and appreciate the contribution.¹ While we agree with some of the data presented, clarifications are necessary. A recent clinical licensing trial showed similar species distribution compared to historical data, which contradicts the suggestion that *C. parapsilosis* is increasing.² Large epidemiological studies over the last several years also suggest a relatively stable rate of non-*albicans* *Candida*.³

While most non-*albicans* *Candida* are associated with high antifungal minimum inhibitory concentrations (MIC), *C. parapsilosis* is typically susceptible to most antifungals. However, *C. parapsilosis* is associated with higher echinocandin MIC that vary between agents.^{4,5} In vivo studies demonstrate that high echinocandin doses yield reductions of colony-forming units that are 100-fold less for *C. parapsilosis* than *C. albicans*.⁵ Extrapolation to all agents may not be reliable as suggested in the presented data.

In published studies, we agree that few patients with *C. parapsilosis* have been assessed, however, not stated was that one can miss critical differences in clinical response. In one licensing trial, 19% of patients were infected with *C. parapsilosis*. Although caspofungin was clinically effective, 42% of treated patients with persistent fungemia had this *Candida* subspecies.⁶ The rate of persistently positive patients in a second study

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was reported as almost double for *C. parapsilosis* versus other *Candida* species.⁷ In a third study, there were as many non-responders with *C. parapsilosis* as responders.⁸ Broader implications could be imagined in immunocompromised patients where clinical responses are poorer.

In conclusion, we are concerned about combining the echinocandins in this recommendation. Grouping these agents into one treatment cohort is difficult due to the variability in microbiological responses seen between agents.⁹ Significantly powered studies designed to evaluate clinical responses in patients with *C. parapsilosis* are not available and need to be performed before universally recommending an echinocandin for candidemia due to *C. parapsilosis*.

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Authors' Response

We appreciate the comments by Drs. Stover and Cleary. While there may be stable rates of non-albicans *Candida* in some settings, the most current SENTRY analysis reports increase blood stream infections due to *Candida parapsilosis* (CP) in the institutional settings and in a US population-based surveillance.¹⁻³

Although there may be differences in pharmacokinetic parameters in the three echinocandins, their pharmacodynamic activity against *Candida* appears to be consistent.⁴ Among 215 CP isolates, tested in the SENTRY data base, there were no resistant isolates.¹ Among 162 CP isolates the main MIC₅₀ ranged from 1–2 for the echinocandin group.⁵ As the echinocandins have similar pharmacologic properties and in vitro activity against *Candida* species, higher rates of clinical failure are not expected with the echinocandins versus other drug classes. Hence we grouped the echinocandins together (caspofungin, micafungin and anidulafungin).

The issues regarding microbiologic failure and persistence of candidemia mentioned by the authors deserve further consideration. In the licensing trial comparing caspofungin and amphotericin in which 55.6% (5/9) patients with persistent candidemia were CP, no logistic regression analysis was provided to ensure that these differences were not related to host factors or underlying source.⁶ In addition among 7 patients in the caspofungin group with recurrent episodes of candidemia, none were due to CP. Finally, 80% (4/5) of these isolates were from a single study site and 12 of 14 patients with CP infections at other sites were successfully treated with caspofungin.

In the study by Colombo and colleagues comparing caspofungin and comparator drugs, 17% (12/70) of CP patients had persistent

positive cultures as reason for failure compared with 6.4% (19/295) of other *Candida spp.*⁷ However, the median time to clearance of blood cultures for CP was 2.5 days, which was similar to all other species tested.

We acknowledge the limitations of using meta-analysis data for treatment recommendations of subgroups of larger studies. It would be difficult to develop prospective randomized studies that are adequately powered to answer the question of relative efficacy of echinocandins compared with other antifungal agents in CP infections. This meta-analysis shows that although there may be in vitro differences in potency of the echinocandins against CP compared to other *Candida* species, there was no significant difference in treatment outcomes based on pooled analysis. Based on existing data, echinocandins do not appear to be clinically inferior to comparator drugs for the treatment of CP candidemia.

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