Prophylactic Echinocandin: Is There a Subgroup of Intensive Care Unit Patients Who Benefit?

Eavan G. Muldoon and David W. Denning

The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, United Kingdom

(See the Major Article by Ostrosky-Zeichner et al on pages 1219–26.)

Keywords. caspofungin; micafungin; anidulafungin; candidaemia; peritonitis.

Prevention of fungal infection in at-risk patients is an established medical practice. Establishing the optimal combination of antifungal agent with the highest at-risk group has been the subject of hundreds of studies. Given the mortality associated with invasive candidiasis (IC) in the intensive care unit (ICU), a prophylactic approach to antifungal therapy is attractive, but little studied, other than in certain patient subgroups, such as liver transplant recipients and neonates. In general ICU patients, only fluconazole has been studied and probably has a role in those at high risk of developing *Candida* peritonitis, and by implication those with pancreatitis [1]. In this issue of *Clinical Infectious Diseases*, Ostrosky-Zeichner et al have authored the first multicenter trial (MSG-01) in a larger group of at-risk patients and utilize the echinocandin caspofungin, a broader-spectrum agent than fluconazole, as antifungal prophylaxis. Overall, their results do not show a benefit in these at-risk ICU patients. Based on this study, prophylactic use of caspofungin cannot be recommended for all at-risk ICU patients to prevent IC.

Identification of at-risk patients is central to prudent use of antifungal prophylaxis in the ICU. There are some uncertainties in MSG-01 related to the selection of at-risk patients. For example, patients undergoing major cardiovascular surgery are at lower risk of IC than those with abdominal surgery, and yet both groups are lumped together under "major surgery"; 14% of the patients had cardiovascular surgery and only 11% had gastrointestinal surgery. Furthermore, the authors use a prediction rule that they had developed previously to identify at-risk patients; this prediction rule excludes solid organ transplant recipients, and yet in the current article corticosteroid therapy is considered a risk categorization and there is no mention of transplantation. In addition, the incidence of IC in patients identified using this prediction rule is lower in both groups (prophylaxis and placebo) than expected. Taken together, these features of the current study make the utility of the findings difficult to translate.

The authors utilize the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) diagnostic criteria for determination of proven and probable cases of IC. However, these criteria were specifically developed for immunocompromised patients, not ICU patients. Indeed, the authors of the EORTC/MSG criteria explicitly cautioned against using the probable criteria in ICU patients. An alternative approach would have been to use the criteria as described by Eggiman et al or Senn et al, which identified patients who could benefit from the use of antifungal prophylaxis in the ICU [2, 3]. In addition, in the current study, the criteria for the diagnosis of *Candida* peritonitis are not clearly defined; this is an important and tricky diagnosis in ICU patients and open to both over- and underdiagnosis. In a large multicenter ICU study in France, there were approximately 2 cases of candidemia for every 1 case of *Candida* peritonitis, with only a minority of the latter having positive blood cultures [4]. Furthermore, fluconazole (and presumably caspofungin) reduces diagnostic yield from blood culture in patients with autopsy demonstration of IC [5]. The combination of an imprecise definition of *Candida* peritonitis and "false negative" blood cultures may have led to the apparent nonsignificant reduction in IC. This could account for the lack of survival benefit. Whereas the use of β-1,3-D-glucan to aid in the diagnosis of proven and probable IC is appropriate and

Received 9 January 2014; accepted 13 January 2014; electronically published 18 February 2014.

Correspondence: David W. Denning, FRCP, National Aspergillosis Centre, Wythenshawe Hospital, Southmoor Road, Manchester M23 9LT, UK (ddenning@manchester.ac.uk).

Clinical Infectious Diseases 2014;58(9):1227–9

© The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciu080

Downloaded from https://academic.oup.com/cid/article/58/9/1227/365851 by guest on 20 April 2021

welcomed, unfortunately, no comparison of β-1,3-D-glucan values in the 2 arms of the study is provided.

This MSG-01 study underscores the existing literature on the morbidity associated with IC; patients with proven and probable IC had significantly longer lengths of ICU stay. The importance of early treatment of IC has already been documented [6]. Ostrosky-Zeichner et al report that a "preemptive approach" in managing at-risk ICU patients was associated with a lower incidence of proven or probable IC. However, the terminology used is somewhat confusing. This preemptive group is merely all patients enrolled in the study of caspofungin prophylaxis, including those who were excluded due to proven or probable IC at baseline, whereas the term "preemptive" has historically referred to identification of a specific risk marker such as a high cytomegalovirus polymerase chain reaction (PCR) posttransplant or *Candida tropicalis* in the stool of a neutropenic patient. Drawing conclusions from this group seems dangerous, particularly if these data are used to promote antifungal prophylaxis in the ICU. Although the authors assert that including these patients complies with the intent and concept of preemptive therapy, the study is not designed to truly evaluate a preemptive approach, as they used the incidence of proven or probable IC as their outcome. A further multicenter study of screening using newer diagnostic techniques would be required to answer the question of whether a truly preemptive approach (ie, commencement of antifungal therapy in at-risk patients, followed by close follow-up and discontinuation of antifungal therapy if IC is excluded) impacts patient outcomes and would have far greater clinical implications. Real-time PCR may ultimately prove to be a better screening and diagnostic tool than β-1,3-D-glucan [7].

Although prophylactic use of antifungal therapy is attractive, particularly as the incidence of IC in ICU patients increases, there may be longer-term epidemiological considerations. Caspofungin was licensed in the United States in 2001, and to date the development of echinocandin resistance among *Candida* species has been rare, possibly leading to complacency about the ability of *Candida* species to circumvent echinocandin therapy. Recently published is the emergence of high rates of echinocandin resistance (>12%) in already fluconazole-resistant *Candida glabrata* clinical isolates [8, 9]. Loss of susceptibility to echinocandins in *Candida* species leaves only amphotericin B (with or without flucytosine) for treatment, which is not an ideal agent in critically ill ICU patients. It has also been shown that with the increasing use of fluconazole, the epidemiology of *Candida* species in the hospital setting changes due to selective pressure. Fluconazole-resistant *Candida* species (notably *C. glabrata* and *C. krusei*) become more prevalent [10]. More recent reports of the emergence of rare, multidrug-resistant *Candida* species [11] should ring alarm bells regarding antifungal overuse. Therefore, not only does the lack of benefit overall clearly indicate that caspofungin should not be used as a prophylactic agent, the emergence of resistant *Candida* species also speaks against this approach.

An additional important consideration in modern healthcare settings, especially in the world's most expensive healthcare system—the United States—is that of cost. The average wholesale price of both the loading and daily maintenance doses of caspofungin is more than $400. A prophylactic approach such as the one studied in this study would need to demonstrate clear benefit to justify such cost, and it does not.

At this time, prophylaxis with antifungal agents in ICU patients should be limited to the patient populations in which it has been shown to have proven benefit (post–gastrointestinal perforation; severe pancreatitis; liver, pancreas, and/or small bowel transplant; extremely low birth-weight neonates) [1]. There are important implications for the development of antifungal resistance and cost, despite the tolerability of caspofungin, should a strategy of prophylaxis be pursued. Further study is warranted on the use of newer diagnostic techniques coupled with a truly preemptive approach to the use of antifungal therapy in ICU patients. Strategies such as these may impact mortality in IC in the ICU, and we await the outcome of well-conducted clinical studies to evaluate them.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Charlier C, Hart E, Lefort A, et al. Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? J Antimicrob Chemother **2006**; 57:384–410.
2. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. Crit Care Med **1999**; 27:1066–72.
3. Senn L, Eggimann P, Ksontini R, et al. Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients. Intensive Care Med **2009**; 35:903–8.
4. Montravers P, Mira JP, Gangneux JP, Leroy OLortholary O. A multicentre study of antifungal strategies and outcome of *Candida* spp. peritonitis in intensive-care units. Clin Microbiol Infect **2011**; 17:1061–7.
5. Kami M, Machida U, Okuzumi K, et al. Effect of fluconazole prophylaxis on fungal blood cultures: an autopsy-based study involving 720 patients with haematological malignancy. Br J Haematol **2002**; 117:40–6.
6. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis **2006**; 43:25–31.
7. Nguyen MH, Wissel MC, Shields RK, et al. Performance of *Candida* real-time polymerase chain reaction, beta-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. Clin Infect Dis **2012**; 54:1240–8.
8. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis **2013**; 56:1724–32.

Downloaded from https://academic.oup.com/cid/article/58/9/1227/365851 by guest on 20 April 2021

9. Liu W, Tan J, Sun J, et al; China-SCAN team. Invasive candidiasis in intensive care units in China: in vitro antifungal susceptibility in the China-SCAN study. J Antimicrob Chemother **2014**; 69:162–7.

10. Chow JK, Golan Y, Ruthazer R, et al. Factors associated with candidemia caused by non-albicans *Candida* species versus *Candida albicans* in the intensive care unit. Clin Infect Dis **2008**; 46:1206–13.

11. Chowdhary A, Anil Kumar V, Sharma C, et al. Multidrug-resistant endemic clonal strain of *Candida auris* in India [published online ahead of print 20 December 2013]. Eur J Clin Microbiol Infect Dis **2013**.

Downloaded from https://academic.oup.com/cid/article/58/9/1227/365851 by guest on 20 April 2021