Commentary

Empiric anti-*Candida* therapy for patients with sepsis in the ICU: how little is too little?

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See related research by Zilberberg *et al*., http://ccforum.com/content/13/3/R94

Abstract

Prior analyses suggest that empiric fluconazole for ICU patients with sepsis is cost-effective. Using updated estimates of efficacy and cost, Zilberberg and colleagues compare the use of micafungin with that of fluconazole. The authors conclude that micafungin is an attractive alternative to fluconazole. This conclusion is driven by recent reduction in micafungin's cost and by better activity of micafungin against azole-resistant *Candida* species. Their results are limited by inflated estimates of efficacy, life expectancy and risk of *Candida* sepsis. This commentary explores the rationale for early anti-*Candida* strategies in the ICU and highlights the contribution and limitations of the article by Zilberberg and colleagues.

In their article in *Critical Care*, Zilberberg and colleagues examine the cost-effectiveness of empiric anti-*Candida* treatment for ICU patients with sepsis [1]. Over the past decade, *Candida* has emerged as an invasive pathogen in many ICUs [2-4]. The case-fatality rate for *Candida* blood-stream infections is substantially higher than that for bacterial blood-stream infections [5]. Exploring the reasons for such a trend, Kumar and colleagues [6] compared a large number of severe sepsis episodes caused by bacteria or *Candida*. Despite their high severity of illness and in contrast to patients with bacterial sepsis, most of those with *Candida* sepsis did not receive effective treatment within 24 hours of hypotension. Although the overall case-fatality rate was higher among those with *Candida* sepsis, the case-fatality rate among those who received early anti-*Candida* therapy was substantially lower and comparable to that seen in bacterial sepsis [6]. These data suggest that the early initiation of empiric anti-*Candida* treatment is life saving.

The initiation of empiric anti-*Candida* therapy to patients with sepsis represents a tradeoff. On one hand, it can increase the survival rate among those infected with *Candida*. On the other hand, it increases costs and, possibly, the risk of drug-related toxicity, drug-drug interactions, and emergence of antifungal resistance [7]. Clinicians caring for ICU patients with sepsis frequently wonder in which circumstances is the administration of an empiric anti-*Candida* agent advisable? Which agent is most attractive? Similar to other clinical questions, the best experimental design to evaluate treatment strategies is the clinical trial. But like any trial that evaluates an empiric strategy, the required sample size, and, therefore, the cost and ability to enroll enough patients, are often prohibitive. When data from clinical trials are not available, an alternative research design needs to be utilized.

Decision analysis is used to compare the effectiveness and cost of alternative interventions and to identify the most effective strategy that has an acceptable cost-effectiveness ratio. When reliable data are available and standard methodology is employed, the results of decision analysis can help guide clinicians. The epidemiology of bacterial and *Candida* sepsis in the ICU is well described and estimates of the effectiveness and cost of anti-*Candida* agents are available. Thus, questions such as those related to the initiation of empiric anti-*Candida* agents in the ICU can be answered using decision analysis.

Because *Candida* is only one of several pathogens that cause sepsis in ICU patients, the empiric administration of an anti-*Candida* agent would result in exposure to anti-*Candida* therapy for many patients with non-*Candida* sepsis. While only those with *Candida* sepsis can benefit, all can be harmed by toxicity. Thus, to be considered a reasonable candidate, the anti-*Candida* agent should have low toxicity. In the past, the benefit from antifungals such as amphotericin deoxycholate or its lipid preparations was balanced by substantial toxicity [7-8]. With the recent availability of safer anti-*Candida* agents, the triazoles and echinocandins, empiric therapy became a viable approach. A 2005 analysis determined that the empiric use of a safe anti-*Candida* agent would increase the survival of ICU patients with suspected

infection and no response to three days of anti-bacterials [8]. In that analysis, empiric caspofungin was the most effective strategy but its cost in 2005 was high, resulting in empiric fluconazole as the preferred strategy. Several critical factors have changed since 2005. Additional echinocandins have been approved, their cost has substantially decreased, and, in many ICUs, isolates of *Candida* from blood-stream infections are now less susceptible to fluconazole [2]. Thus, the article by Zilberberg and colleagues, which uses current estimates, is relevant and timely.

Zilberberg and colleagues conclude that empiric micafungin is a cost-effective alternative to empiric fluconazole. Given that both agents have low toxicity, this conclusion is driven by differences in drug cost and in efficacy. The authors calculated that empiric micafungin saves more lives than empiric fluconazole. This better efficacy is based on the assumption that micafungin is active against fluconazole-resistant *Candida* species. The authors consider *Candida krusei* or *Candida glabrata* as fluconazole resistant. But data from clinical trials show that 50 to 60% of *C. glabrata* isolates are treatable by fluconazole when administered at the dose used in Zilberberg and colleagues' analysis [9-10]. As a result, the estimate used in Zilberberg and colleagues' analysis inflates the efficacy difference and biases the analysis in favor of micafungin.

Additional factors that determine the cost-effectiveness of empiric anti-*Candida* strategies are the proportion of ICU sepsis that is caused by *Candida* and the life-expectancy of *Candida* sepsis survivors. For both, larger estimates support the use of costly anti-*Candida* agents. The authors assume that 14% of ICU sepsis episodes are caused by *Candida*. This estimate is higher than the 5 to 10% estimate described in recent literature and is based upon studies that included the isolation of *Candida* from the lungs and other clinically irrelevant sites as representing '*Candida* sepsis' [2,6,11]. To estimate the life expectancy of an ICU survivor, the authors use actuarial tables that reflect life expectancy in the general population, and adjust them for increased mortality related to sepsis. But survivors of an ICU-acquired sepsis have a substantially lower life expectancy compared to age-matched representatives of the general population [12,13]. These over-estimations exaggerate the affordability of empiric micafungin.

Nevertheless, the main finding of this study by Zilberberg and colleagues is encouraging. The reduction in the acquisition cost of micafungin, as well as that of other echinocandins, has made these effective anti-*Candida* agents more affordable. Additional data and improved estimates will help refine the best empiric anti-*Candida* strategy for ICU patients with sepsis.

Competing interests

YG has received research funding and is on the advisory board for Merck and Pfizer. YG is also a consultant and on the speakers' bureau for Merck and Astellas Pharmaceuticals.

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