Marin H. Kollef
José-Artur Paiva
Pierre-Emmanuel Charles

Candidemia and non-candidemia related septic shock: are there differences between them?

Received: 30 April 2014
Accepted: 2 May 2014
Published online: 16 May 2014
© Springer-Verlag Berlin Heidelberg and ESICM 2014

M. H. Kollef (✉)
Division of Pulmonary and Critical Care Medicine, Washington
University School of Medicine, 660 South Euclid Avenue,
Campus Box 8052, St. Louis, MO 63110, USA
e-mail: mkollef@dom.wustl.edu
Tel.: (314) 454-8764

J.-A. Paiva
Emergency and Intensive Care Department, Centro Hospitalar
S. João EPE, Faculdade de Medicina, University of Porto, Porto,
Portugal

P.-E. Charles
Service de Réanimation Médicale, Hôpital Bocage Central, CHU
Dijon, 14 rue Gaffarel, BP 77908, 21079 Dijon Cedex, France

In a recent issue of *Intensive Care Medicine*, Bassetti and colleagues [1] evaluated 216 patients with septic shock attributable to *Candida* bloodstream infection from five teaching hospitals in Italy and Spain. Overall, 116 patients (53.7 %) died within 30 days from the onset of *Candida* bloodstream infection. Multivariate logistic regression analysis demonstrated that inadequate source control, inadequate antifungal therapy, and increasing severity of illness measured by APACHE II scores were independently associated with greater 30-day mortality. Initial treatment was considered adequate if the infecting organism was susceptible to the prescribed antimicrobial regimen and the dosage of antifungal used was adequate within the first 24 h from culture positivity.

The results of this study confirm the findings of Kollef et al. [2] who identified 224 consecutive patients with septic shock and a positive blood culture for *Candida* from St. Louis, Missouri. Overall hospital mortality occurred among 155 (63.5 %) patients. Similar to the study above, multivariate logistic regression analysis demonstrated that delayed antifungal treatment and failure to achieve timely source control were independently associated with a greater risk of hospital mortality. Antimicrobial treatment was classified as adequate if the prescribed antibiotic regimen included an antifungal agent directed against the isolated *Candida* species and was administered within 24 h of the onset of septic shock. Despite differences in the definition employed for adequate antifungal therapy, these studies, like others [3–5], emphasize the importance of timely treatment with antifungal agents and source control in *Candida* septic shock in order to optimize patient outcomes.

It is also important to note that several recent investigations were unable to identify a beneficial association between the timing of antifungal therapy and mortality in patients with *Candida* bloodstream infection [6, 7]. This could be explained by the reported greater clinical efficacy of echinocandins in this setting as compared with fluconazole, potentially minimizing the deleterious effect of delayed therapy [8]. However the rationale in favor of early adequate antifungal therapy seems indisputable, especially in patients with septic shock. Kumar et al. [9] reported that patients with septic shock attributed to *Candida* infection were more likely to have a greater than 12-h delay in the initiation of effective antimicrobial therapy compared to septic shock attributed to bacterial etiologies (74.7 vs. 26.3 %) accounting, in large part, for the greater mortality associated with septic shock attributed to *Candida* infection (82.5 vs. 52.3 %).

The changing outcomes associated with septic shock are illustrated by a recent report from Australia and New Zealand suggesting that the mortality of septic shock has

decreased over the past 10–15 years as a result of improved supportive care [10]. This is consistent with the findings from the ProCESS trial reporting one of the lowest observed mortality rates for septic shock in their control arm at 18.9 % [11]. Yet over the same time period, the mortality of septic shock attributed to *Candida* remained around 50 % in both the European and St. Louis studies [1, 2]. Potential explanations for this discrepancy include greater severity of illness, co-morbidities, and immune compromise among patients developing infection with *Candida* species. Unfortunately, these are issues the clinician is unable to modify. In contrast, delays in the administration of adequate antifungal therapy and source control are two processes of care that are potentially modifiable.

The use of antifungals, especially echinocandins, as part of empirical antimicrobial therapy in patients with septic shock is a matter of great concern to intensivists trying to balance the trade-offs between unnecessary treatment and delaying appropriate antifungals. It is worth noting that just like in the Bassetti et al. [1] study, most reports showed that only the minority of patients (i.e., <40 %) are already receiving antifungal agents before blood culture positivity is known [2–4]. The so-called Fongiday French survey demonstrated that most of the antifungals started in the ICU were given to the wrong patients [12]. Moreover, several studies aimed at evaluating prophylactic or empirical antifungal therapy strategies in selected high-risk patients according to “rough” clinical criteria (i.e., previous exposure to antibiotics, sustained ICU stay, mechanical ventilation) failed to demonstrate any clinical advantage with such approaches, illustrating our current inability to administrate the right drug to the right patient [13, 14].

Although we do not yet have clear answers as to the best approach for optimizing the administration of antifungal therapy and source control, the adverse consequences associated with delayed therapy of severe sepsis/septic shock complicating candidemia have resulted in the development of innovative diagnostic and therapeutic approaches. Tissot et al. [15] recently evaluated several strategies for the empiric treatment of life-threatening intra-abdominal candidiasis (IAC) in high-risk surgical ICU patients. They found that 1,3- β -D-glucan antigenemia was superior to the use of the *Candida* score and colonization indexes for the diagnosis of blood culture-negative IAC and to direct antifungal therapy in this high-risk surgical ICU population. Alternatively, novel rapid diagnostic platforms are being developed that hold the promise for swift and accurate diagnosis of *Candida* bloodstream infection, potentially obviating the need for microbiologically undirected empiric therapy [16]. However, such diagnostic techniques are likely years from being universally available, suggesting that an empiric or preemptive treatment approach in patients with septic shock at high risk of *Candida* infection may be reasonable at the present time. Moreover, further studies are needed to prospectively assess the clinical relevance of such strategies, especially in the “medical” patient population whose mortality could be even worse in the setting of delayed treatment of candidemia, as source control—a key issue in their management—often cannot be achieved in most of these patients in which yeast translocation into the bloodstream is due to gut failure.

For patients whose septic shock could be attributed to *Candida*, on the basis of the source of infection (intra-abdominal or catheter) and underlying risk factors (known *Candida* colonization, total parenteral nutrition,

Fig. 1 Management pathway for patients with septic shock

prolonged antibiotic exposure, upper digestive tract surgery), especially in healthcare-associated infections, empiric antifungal therapy seems reasonable as long as it is associated with a de-escalation of antifungal treatment based on negative microbiology results. In the future, rapid and accurate molecular diagnostic methods may become available to more accurately guide our

management of septic shock in order to minimize the administration of inadequate antimicrobial therapy and to avoid unnecessary antimicrobial exposure (Fig. 1).

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Bassetti M, Righi E, Ansaldi F, Merelli M, Cecilia T, De Pascale G, Ana Diaz-Martin A, Luzzati R, Rosin C, Lagunes L, Trecarichi M, Sanguinetti M, Posteraro B, Garnacho-Montero J, Sartor A, Rello J, Della Rocca G, Antonelli M, Tumbarello M (2014) A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. *Intensive Care Med*. doi: [10.1007/s00134-014-3310-z](https://doi.org/10.1007/s00134-014-3310-z)
2. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A (2009) Septic shock attributed to Candida infection: importance of empiric therapy and source control. *Clin Infect Dis* 54:1739–1746. doi: [10.1093/cid/cis305](https://doi.org/10.1093/cid/cis305)
3. Labelle AJ, Micek ST, Roubinian N, Kollef MH (2008) Treatment-related risk factors for hospital mortality in Candida bloodstream infections. *Crit Care Med* 36:2967–2972. doi: [10.1097/CCM.0b013e31818b3477](https://doi.org/10.1097/CCM.0b013e31818b3477)
4. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, Bearden DT (2006) Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 43:25–31
5. Patel GP, Simon D, Scheetz M, Crank CW, Lodise T, Patel N (2009) The effect of time to antifungal therapy on mortality in Candidemia associated septic shock. *Am J Ther* 16:508–511
6. Grim SA, Berger K, Teng C, Gupta S, Layden JE, Janda WM, Clark NM (2012) Timing of susceptibility-based antifungal drug administration in patients with Candida bloodstream infection: correlation with outcomes. *J Antimicrob Chemother* 67:707–714
7. Kludze-Forson M, Eschenauer GA, Kubin CJ, Della-Latta P, Lam SW (2010) The impact of delaying the initiation of appropriate antifungal treatment for Candida bloodstream infection. *Med Mycol* 48:436–439
8. Tumbarello M, Posteraro B, Trecarichi EM, Fiori B, Rossi M, Porta R, de Gaetano Donati K, La Sorda M, Spanu T, Fadda G, Cauda R, Sanguinetti M (2007) Biofilm production by Candida species and inadequate antifungal therapy as predictors of mortality for patients with candidemia. *J Clin Microbiol* 45:1843–1850
9. Kumar A, Skrobik I, Guzman J, lapinsky S, Llaupland K, CATSS Database Research Group (2007) The high mortality of Candida septic shock is explained by excessive delays in initiation of antifungal therapy. Poster K-2174, 47th ICAAC, Chicago, Illinois
10. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 311:1308–1316. doi: [10.1001/jama.2014.2637](https://doi.org/10.1001/jama.2014.2637)
11. The ProCESS Investigators (2014) A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 370(18):1683–1693
12. Azoulay E, Dupont H, Tabah A, Lortholary O, Stahl JP, Francois A, Martin C, Guidet B, Timsit JF (2012) Systemic antifungal therapy in critically ill patients without invasive fungal infection. *Crit Care Med* 40:813–822. doi: [10.1097/CCM.0b013e318236f297](https://doi.org/10.1097/CCM.0b013e318236f297)
13. Schuster MG, Edwards JE Jr, Sobel JD, Darouiche RO, Karchmer AW, Hadley S, Slotman G, Panzer H, Biswas P, Rex JH (2008) Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. *Ann Intern Med* 149:83–90
14. Ostrosky-Zeichner L, Shoham S, Vazquez J, Reboli A, Betts R, Barron MA, Schuster M, Judson MA, Revankar SG, Caeiro JP, Mangino JE, Mushatt D, Bedimo R, Freifeld A, Nguyen MH, Kauffman CA, Dismukes WE, Westfall AO, Deerman JB, Wood C, Sobel JD, Pappas PG (2014) MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. *Clin Infect Dis* 58:1219–1226. doi: [10.1093/cid/ciu074](https://doi.org/10.1093/cid/ciu074)
15. Tissot F, Lamoth F, Hauser PM, Orasch C, Flückiger U, Siegemund M, Zimmerli S, Calandra T, Bille J, Eggimann P, Marchetti O, Fungal infection network of Switzerland (FUNGINOS) (2013) β -Glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am J Respir Crit Care Med* 188:1100–1109. doi: [10.1164/rccm.201211-2069OC](https://doi.org/10.1164/rccm.201211-2069OC)
16. Zhang SX (2013) Enhancing molecular approaches for diagnosis of fungal infections. *Future Microbiol* 8:1599–1611. doi: [10.2217/fmb.13.120](https://doi.org/10.2217/fmb.13.120)