Candidemia in the Intensive Care Unit

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KEYWORDS

• Candidemia • Invasive candidiasis • *Candida* • Intensive care unit • Critical care • Fungal infection

KEY POINTS

- *Candida* is the most common invasive mycosis in critically ill patients.
- Candidemia in the intensive care unit extends the length of stay, increases health care costs, and carries a high crude mortality.
- The contribution of non-albicans *Candida* species to this infection is on the rise.
- The role of antifungal administration before culture confirmation of candidemia in critical care units remains debatable.
- Echinocandins are the drug class of choice for the treatment of established intensive care unit candidemia.

INTRODUCTION

Invasive candidiasis (IC), distinct from localized, mucocutaneous candidiasis, is a prevalent and burdensome infection of particular importance to intensive care unit (ICU) physicians. Its initial association with chemotherapy-induced neutropenia has progressively widened to encompass a broad spectrum of ICU patients in parallel with advances in organ support techniques, therapeutic immunosuppression, and antibacterial pharmacotherapy. Candidemia, the most common means by which IC is diagnosed clinically, is the principal focus of this review, although it should be borne in mind that organ involvement can take on many forms, including peritoneal, ocular, pulmonary, and central nervous system manifestations. IC presents several challenges to the ICU community. Recognition and, therefore, treatment of this infection are frequently delayed, with dramatic clinical deterioration and death often preceding the detection of *Candida* in blood cultures. Identification of individual patients at highest risk for developing candidemia remains an imperfect science, and the role of untargeted (ie, before microbiological confirmation) antifungal therapy in the ICU is yet to be fully defined. Antifungal resistance among typical *Candida* isolates and the emergence of novel, multi-drug-resistant species such as *Candida auris* complicate therapeutic decision making. The absence of well-established molecular techniques for early detection of candidemia hinders efforts to reduce the heavy clinical and economic impact of this infection. What follows is a review of nonneutropenic candidemia in the ICU with an emphasis on the aforementioned diagnostic and management challenges.

EPIDEMIOLOGY

Background

Candida is the most common invasive fungus in critically ill patients, and the candidemia rate in ICUs is about 10 to 20 times that of non-ICU

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settings.[1,2] Among critical care areas, the highest incidence belongs to burn units.[3] Candidemia can impose a significant operational and budgetary burden on an ICU: it was shown to prolong ICU stay by nearly 13 days in one study while adding an estimated $8570 (€7800) in attributable costs in another, driven primarily by sepsis treatment itself.[4,5] Although more than 15 species of Candida have been implicated in human disease, almost all episodes of candidemia can be ascribed to 1 of 5 species: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei* (**Table 1**). *C albicans* is the most prevalent isolate globally, responsible for approximately 40% to 60% of cases.[6,7] In a growing number of reports, particularly more contemporary ones, *C albicans* constitutes the minority of *Candida* isolates.[6,8,9] The most prevalent non-albicans species varies geographically. In European and Australian ICUs, *C glabrata*, less virulent than *C albicans* and associated with increasing age and solid organ transplants, is generally the most common non-albicans isolate, accounting for about 20% of infections.[2,3,10] Isolation of *C tropicalis*, which is on par with *C albicans* in terms of virulence, is comparatively infrequent (~9%). A 2006 series from an Italian ICU with a large immunosuppressed contingent reported a 23% rate of the hypovirulent *C parapsilosis*, and a very recent Chinese ICU cohort representing diverse pathology recapitulated the same finding.[9,11,12] In South America, on the other hand, these proportions are reversed: *C tropicalis* is the most common non-albicans isolate (~20%), whereas *C glabrata* accounts for 9%.[13] These differences in species distribution may help explain the disparate ICU candidemia crude mortality figures reported from Europe and South America: 50% and 70%, respectively.[7,10,13] Determining the attributable mortality of ICU candidemia, the net contribution of this infection to mortality beyond that expected from overall clinical status, is hampered by a paucity of data and lack of patient matching. In a retrospective, matched cohort study of Belgian ICU patients with high critical illness scores (mean Acute Physiology and Chronic Health Evaluation [APACHE] II of 25), the attributable mortality of candidemia was only 5% in comparison to 20% for a likewise matched Chinese surgical ICU population with severe sepsis and lower APACHE scores.[14,15] Studied prospectively, a global ICU cohort exhibited a nonsignificant difference of less than 5% in hospital mortality between candidemic and noncandidemic subjects after propensity score matching.[16] On the other hand, attributable mortality as high as 49% was observed in a case-control study of non-ICU candidemic adults.[17] Possible reasons for the disparity between results within and outside the ICU include earlier and more appropriate initiation of therapy in the ICU as well as the greater baseline disease severity of the critically ill, which reduces the incremental significance of any individual contributor.[18] Differences in local practices, patient types, severity of illness, and study periods may similarly account for contrasting attributable mortalities across ICU studies.

Albicans versus Non-Albicans Species

The shifting epidemiology of *Candida* toward non-albicans species reported by some, although not all, institutions is clinically relevant because of the high rates of fluconazole resistance among *C glabrata* isolates and the intrinsic fluconazole resistance of *C krusei*.[19,20] This development has

Table 1
Epidemiologic and clinical characteristics of the 5 most common *Candida* species

Species	Geographic Concentration	Age Predilection	Relative Virulence	Characteristic Clinical Associations	Fluconazole Susceptibility
C albicans	Global	None	High	Endophthalmitis	+++
C glabrata	Europe, US, Australia	Older	Intermediate	SOT	+
C tropicalis	SA, US, Asia	None	High	Immunosuppression	++
C parapsilosis	Europe, SA, Australasia	Younger	Low	Medical devices	+++
C krusei	Europe, US	None	Intermediate	Hematological malignancy	–

Abbreviations: SA, South America; SOT, solid organ transplant.
Data from Refs.[37,116–120]