Is *Candida* really a threat in the ICU?

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Purpose of review

The epidemiological and clinical relevance of *Candida* in the ICU is reviewed. Three issues were appraised. First is the prevalence of *Candida*. Second is the relevance of nonblood cultures positive for *Candida* and multisite colonization. Third is the importance of invasive candidiasis in terms of mortality.

Recent findings

The diagnosis of invasive candidiasis remains problematic in nonblood cultures. Consequently, the true prevalence of invasive candidiasis is difficult to assess. Another result of the complicated diagnosis is the risk for delayed antifungal therapy in case of systemic *Candida* infection. Therefore, pre-emptive therapy has become increasingly popular in high-risk patients.

Summary

Candida spp. cause a minority of nosocomial bloodstream infections (~4–9%). Yet, delayed initiation of appropriate antifungal therapy results in significant attributable mortality. Given the inability to efficiently discriminate colonization from invasive candidiasis, this is a problematic issue. The presence of *Candida* in tracheal aspirates, urine cultures or wound swabs frequently reflects colonization. Yet, multisite colonization frequently precedes systemic invasion. As such, multisite *Candida* colonization is a crucial element in the decision to start pre-emptive therapy. However, the predictive value of multisite colonization in the absence of an overt risk profile for invasive candidiasis appears to be low.

Keywords

antifungals, *Candida*, diagnosis, intensive care, mortality, outcome

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Introduction

In the past decades, *Candida* has evolved as a major infectious issue in ICU patients [1]. The problem of *Candida*, however, can easily be overestimated. First, with the exception of candidemia, the diagnosis of invasive candidiasis is difficult, which may result in an overestimation of the incidence, and in injudicious use of antifungals. Second, *Candida* is an opportunistic pathogen favoring hosts with a strongly debilitated physical state. As such, its presence is typically observed in critically ill patients with compromising underlying conditions, who endured multiple invasive procedures, were exposed to different classes of antibiotics, and who experienced prolonged hospitalization periods, due to poorly recovering organ failure. As a consequence, the presence of cultures positive for *Candida* is associated with worse outcomes and often pointed out as a bad omen. The extent to which *Candida* infection contributes to this bad outcome remains a subject of controversy.

In this paper, we balance the importance of *Candida* in ICUs. In this regard, three questions are to be answered: First, what is the relevance of invasive candidiasis in terms of prevalence? Second, what is the relevance of cultures positive for *Candida*? Third, what is the relevance of invasive candidiasis in terms of mortality?

Prevalence of invasive candidiasis

Incidence data on invasive candidiasis are scarce and often unreliable due to the problematic diagnosis. Most incidence data refer to candidemia, but also here incidence data exclusively reporting on ICU patients are limited. In general, the incidence of nosocomial fungal infection amplified dramatically during the 1980s, including a 400% increase in candidemia [2]. Most probably, this was the consequence of favorable progresses in medicine resulting in a growing number of extremely vulnerable patients at risk for opportunistic infections. With the introduction of fluconazole, however, effective antifungal prophylaxis and pre-emptive therapy became possible for high-risk patients. One might assume that this resulted in a significant decrease of candidemia in US ICUs during the 1990s as indicated by the data from the National Nosocomial Infection Surveillance System [3].

This decrease was totally due to a reduction in the number of *Candida albicans* candidemia. As such, a relative increase in candidemia caused by *Candida* nonalbicans was observed during that period. From this, it seems that the growing importance of *Candida* nonalbicans is due to a shift in proportion not necessarily representing a greater number of infections.

Relative to other pathogens causing nosocomial bloodstream infections, *Candida* spp. are of discrete importance, generally causing about 4–9% of the infections [4–10]. Even in a subset of 96 patients with bloodstream infection originating from an intra-abdominal source, De Waele *et al*. [11] found *Candida* spp. to be responsible for causing only 7.3% of infections, although a majority of these high-risk patients probably received antifungal prophylaxis. From this viewpoint, *Staphylococcus aureus*, coagulase-negative Staphylococci, *Enterobacteriaceae*, and nonfermenters such as *Pseudomonas* and *Acinetobacter* spp. are of greater epidemiological importance. Nevertheless, awareness of the problem is mandatory in high-risk patients developing sepsis, as late initiation of antifungal therapy substantially compromises the probability of survival (see below). Despite the rather nonspecific characteristics, high-risk patients are easily recognized. Candidemia typically affects long-term ICU residents with a complicated medical/surgical course. Hence, the problem of candidemia is nearly exclusively valid for the utmost severely ill patients. More specific risk factors for candidemia are described elsewhere [1,12].

The epidemiological relevance of *Candida* in ICUs is also limited by its predominantly endogenous origin. As such, *Candida* is no big issue in infection control as the odds for outbreaks are low. An increased incidence in candidemia, however, should call for a more strict central venous catheter care and handling of parenteral admixtures, especially those containing lipid emulsions.

Relevance of cultures growing *Candida*

With the exception of candidemia, diagnosis of invasive candidiasis is difficult, as it often requires histological confirmation. Although the necessity of antifungal therapy in case of a positive blood culture is generally accepted, the clinical relevance of positive cultures from other body sites is far from clear.

Candida in tracheal aspirates

The isolation of *Candida* spp. from the tracheal tract in mechanically ventilated patients is common (~25%), reflecting, however, colonization of the bronchial tree [13]. The true incidence of invasive disease because of the hematogeneous dissemination and the selective tropism for blood vessels of the lung parenchyma by *Candida* spp. is extremely rare [14–16]. The use of less strict definitions, however, results in a systematic overestimation of the problem. As such, benign *Candida* colonization may be unfairly categorized as *Candida* pneumonia [17,18]. Such practice reflects the extremely difficult confirmation of diagnosis of *Candida* pneumonia because the value of quantitative cultures of respiratory samples is practically unknown, noninvasive diagnostic tools to discriminate colonization from invasive disease are lacking, diseases such as severe coagulation disorders hamper the execution of lung biopsies [13,19]. Furthermore, autopsy studies aimed to estimate the incidence are biased by refusal of next of kin to give the informed consent [20].

Candida in intra-abdominal cultures

The incidence of *Candida* involvement in peritonitis varies depending on the source. Some authors found *Candida* to be the leading or second frequently isolated pathogen in secondary or tertiary peritonitis [21–23]. Yet, in a study of 120 patients with secondary peritonitis, *Candida* was present in only 12% of them, thereby ranking seventh [24]. In ICU patients with secondary or tertiary peritonitis, the significance of *Candida* isolation is controversial [25]. In some studies, the presence of *Candida* was only of little clinical relevance [26], whereas in others the opposite was concluded [18,19]. Microbiological cultures are not straightforward, as these do not distinguish contaminants from true causative pathogens. Only in patients with peroperatively documented *Candida* plaques on the peritoneum, or on histology, a definite diagnosis of *Candida* peritonitis is possible [27]. *Candida*-positive samples taken via drains days after surgery should be interpreted with caution. In the absence of a definite diagnosis, it remains uncertain when it is recommended to initiate antifungal therapy. An algorithm to identify patients with secondary peritonitis that might benefit from antifungal therapy has been proposed [28•]. This algorithm takes into account delay in surgical source control, isolation of *Candida*, presence of severe sepsis or septic shock, and immune status from the patient.

Candiduria

Candida is isolated from urine in about 22% of ICU patients [29]. However, in most instances, this only represents colonization. Candiduria stops in approximately 40% of the patients when the bladder catheter is removed and in 20% when the catheter is removed and replaced [30]. Until today, there is no reliable method to differentiate colonization from infection. High colony counts (>10 000/ml) have been associated with infection in patients without indwelling catheter. Pyuria normally reflects the diagnosis of infection, but it can also be caused either by bacteruria or mucosal trauma by catheterization [31]. *Candida* infection can be ruled out in the absence of pyuria and only low colony counts. The relevance of candiduria is that these patients are

frequently colonized at other body sites as well, thereby increasing the probability of candidemia. Yet, in a study exploring the importance of multiple blood specimens PCR assays in ICU patients with candiduria, the presence of candidal DNA only had a low positive predictive value for candidemia, although with a 100% negative predictive value [32••]. The overall mortality associated with candiduria can reach 50% [33].

Candida in wound cultures

Also in wounds, the presence of *Candida* generally reflects colonization. Topical antiseptic therapy is usually sufficient to prevent higher colony counts and subsequent systemic invasion. In burn wounds, *Candida* deserves special attention. In a recent multicenter observational study of 6918 burn patients, fungal cultures were found in 3.6% of the patients (85% *Candida*), which is in accordance with previous reports [34••,35]. Yet, the occurrence rate of *Candida* colonization is highly dependent on the procedure by which cultures are obtained (routinely or on clinical grounds). *Candida* colonization generally occurs in extremely burned patients with difficultly healing, deep dermal wounds and has a relationship with bad outcome, again indicating its favor for debilitated patients [34••,36]. Following the bath and/or shower procedures, heavily colonized burn wounds are a risk factor for catheter contamination. Importantly, in the study by Ballard *et al.* [34••] colonization of burn wounds was often accompanied by colonization at other body sites and candidemia occurred in nearly one of every six colonized patients. As such, heavy colonization in extremely burned patients can be considered an indication for pre-emptive therapy.

Multisite *Candida* colonization

Due to the problematic diagnosis of invasive candidiasis and the availability of well tolerated antifungal agents, the concept of pre-emptive therapy arise. In this approach, antifungal therapy is administered on the basis of an overt risk profile for invasive candidiasis, but in the absence of sepsis. Pivotal in this strategy is *Candida* colonization at different body sites. Although the clinical relevance of *Candida* colonization at one site is limited (absent?), the relationship between multisite colonization and subsequent development of candidemia has been demonstrated by several investigators [12,37,38••,39]. However, efforts to define a precise cut-off value based on a ratio of cultures positive for *Candida* and the total number of cultures sampled ('colonization index') have been less successful. For example, in a group of 92 medical ICU patients, 36 of whom had a colonization index 0.5 or more, Charles *et al.* [40] only found one patient who subsequently developed invasive candidiasis. More recently, Agvald-Öhman *et al.* [38••] found that seven of 29 patients with a colonization index 0.5 or more developed invasive candidiasis, whereas still three of 30 patients with an index of less than 0.5 developed systemic *Candida* infection as well. Yet, in logistic regression analysis, these authors could demonstrate an increased risk for invasive candidiasis in case of increased colonization density in combination with extensive abdominal surgery. Other investigators also linked the relevance of multisite colonization – and hence the initiation of pre-emptive antifungal therapy – to other significant risk factors [41]. Hence, the initiation of early presumptive therapy should be based on a broad clinical evaluation instead of on multisite *Candida* colonization alone.

Mortality in invasive candidiasis: associated and attributable mortality

The prognosis of critically ill patients with invasive candidiasis or candidemia is dreadful with mortality rates frequently exceeding 40% [42–44]. With the growing proportion of candidemia caused by *Candida* nonalbicans spp., several investigators have compared the mortality of *C. albicans* with *Candida* nonalbicans candidemia [45–48]. In general, *Candida* nonalbicans candidemia occurs more frequently in patients with a somewhat more debilitated condition who were previously exposed to fluconazole [49–51]. In a cohort of ICU patients with *C. glabrata* candidemia, nearly 70% of the patients received fluconazole prior to the candidemia [52•]. Patients with *Candida* nonalbicans candidemia often have a higher mortality. However, no difference in mortality remains after adjustment for disease severity [46–48,53].

In critically ill patients, death due to the infection must be distinguished from death due to severity of disease by means of an appropriate methodological approach [54,55]. Invasive candidiasis has been repeatedly pointed out as an independent predictor of mortality [56–58]. Falagas *et al.* [59] performed a systematic review of matched cohort studies. The attributable mortality rates range from a nonsignificant 5% to a dramatic 71%, with six out of seven studies finding a significantly higher mortality among case patients [60,61]. Only two matched cohort studies estimated the attributable mortality in exclusively ICU patients. In a French multicenter study, Leleu *et al.* [61] reported a significant attributable mortality of 31% in patients with invasive candidiasis. Although using a nearly identical methodology, Blot *et al.* [60] described a nonsignificant attributable mortality rate of 5%. It has been assumed that the high rate of empiric appropriate therapy may have contributed to this favorable result (see below). Unfortunately, Leleu *et al.* [61] could not provide data on antifungal therapy [62].

Importance of empiric appropriate antifungal therapy

Early initiation of appropriate antimicrobial therapy is crucial to lower the attributable mortality in severe sepsis [63•]. Morrell *et al.* [64] demonstrated that failure to

initiate appropriate antifungal therapy within 12 h of blood culture sampling doubled the in-hospital mortality in candidemic patients (adjusted odds ratio (OR): 2.1; 95% confidence interval (CI): 1.5–2.8). Likewise, Parkins *et al.* [65••] found that initiation of appropriate antifungal therapy prior to reporting of the positive culture was independently associated with better survival (OR: 0.46; 95% CI: 0.22–1.00). Similarly, Blot *et al.* [60] found failure to administer the first dose of antifungal therapy within the critical timeframe of 48 h to be an independent predictor of mortality. These data stress the importance of empiric antifungal therapy in patients at risk on the one hand, and the need for rapid diagnostic testing on the other. Regarding the latter, a prospective clinical trial showed promising results of a real-time polymerase chain reaction assay for the diagnosis of candidemia in non-neutropenic ICU patients [66••]. This technique showed high sensitivity and excellent specificity while potentially providing the results the same day.

Another important issue is the increased availability of excellent antifungal agents with favorable safety profiles, such as the azoles voriconazole and posaconazole, and the echinocandins caspofungin, micafungin and anidulafungin. Their broader spectrum might assume a clinical benefit in terms of empiric appropriate therapy rates, and hence survival. This, however, needs to be ascertained.

Conclusion

Candida spp. are frequently isolated from ICU patients with a complicated course. *Candida* isolated from respiratory tract aspirates, urine samples, and wound swabs often reflect colonization and even the presence of *Candida* spp. in intra-abdominal cultures is not necessarily pathogenic. Multisite colonization is a strong predictor for candidemia, especially in combination with other risk factors reflecting severe disease. Due to the problematic diagnosis of invasive candidiasis, it is difficult to estimate the prevalence of the problem. With regard to bloodstream infections, candidemia is caused in only a minority of patients. Nevertheless, awareness of the probability of invasive candidiasis in high-risk patients is necessary as inadequate empiric therapy results in significant excess mortality.

Acknowledgement

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