Candiduria in intensive care units: association with heavy colonization and candidaemia

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Summary Candiduria is increasingly detected in intensive care unit (ICU) patients and often coexists with candidal colonization at other anatomical sites. Studies involving surgical and medical ICU patients have consistently reported a relationship between candiduria and heavy colonization. This suggests that candiduria could be considered as a marker for heavy colonization. Risk factors that predispose to heavy colonization are generally similar to those predisposing to candidaemia. Candiduria in ICU patients is characterized by a high mortality, largely through a significant relationship with candidaemia, which in some patients may reach 50%. Therapeutic interventions should be strongly considered in the critically ill patient who presents with candiduria and concurrent clinical risk factors predisposing to dissemination.

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Introduction Candida species are part of the human microbial flora, with Candida albicans being the most abundant.1,2 Although ubiquitous in nature, candida can also cause various infections primarily in hospitalized patients. Historically, immunosuppressed patients with solid or haematological malignancies have been considered the most susceptible to these infections. With the evolution of intensive care medicine, however, it has become increasingly evident that critically ill patients represent another patient population susceptible to candidal infections. The increased susceptibility of these patients is largely due to use of invasive devices, impaired immune mechanisms due to severe underlying illness and widespread use of antibiotics.3 Invasive candidiasis has been associated with increased morbidity and mortality in ICU patients, which has cost implications since it prolongs ICU and hospital stay.4,5 Prompt diagnosis of candida infection in ICUs is associated with improved...
mortality rates but this is often hampered by the lack of highly sensitive diagnostic tests. Blood cultures, for example, detect only 50% of autopsy-proven candidiasis, and serological methods, although more sensitive, are not widely used. These inherent limitations stress the importance of using clinical parameters and known risk factors associated with invasive candidiasis to make diagnostic and therapeutic decisions.

Candidaemia in ICUs

The term candidaemia is used to indicate acute haematogenous candidiasis that may lead to dissemination. Although by strict definition disseminated candidiasis is not synonymous with candidaemia, we consider the verified recovery of Candida from blood of a critically ill patient as indicative of true candida bloodstream infection. Evidence suggests that the incidence of such infections in ICUs worldwide has increased more than 100% and, in some cases, more than 1000% over the last 30 years. Currently, invasive candidiasis represents 17% of all nosocomial infections. Candidaemia in particular constitutes 5–10% of all bloodstream infections in ICUs. Although C. albicans remains the most common species, there has recently been a shift to other Candida spp., with C. glabrata emerging as the second most frequent isolate.

A comprehensive yet incomplete list of risk factors for candidaemia is shown in Table I. Central venous lines, use of broad-spectrum antibiotics and parenteral nutrition are among the most widely cited. Furthermore, the use of intra-lipid agents in total parenteral nutrition (TPN) formulations, and special classes of antibiotics such as vancomycin or agents targeting anaerobes, seem to further increase the risk of candidaemia in ICU patients. Candidaemia-associated mortality ranges from 35 to 75%. Important clinical variables predicting mortality include severity of underlying disease, manifested as an Acute Physiological Assessment and Chronic Health Evaluation (APACHE) II score ≥21 at the onset of candidaemia and persistently positive blood cultures. Other predictors of mortality are old age, sepsis, chronic obstructive lung disease, multi-organ dysfunction syndrome requiring haemodialysis, non-albicans spp., and severe malnutrition. Delays in diagnosis and/or initiation of effective antifungal treatment are tightly linked to candidaemia mortality. In ICUs where surveillance cultures for Candida are routinely employed and followed by prompt (i.e. within 24 h) initiation of treatment upon unexplained fever, candidaemia does not increase mortality.

Colonization and invasive candidiasis

Colonization refers to presence of Candida spp. in surveillance cultures in the absence of any clinical symptoms or signs of infection. Sites commonly colonized by Candida are the skin, oropharynx, gastrointestinal and urinary tract. More than 50% of ICU patients are known to be colonized with candida and the mortality of multisite candida colonization appears to be as high as that of candidaemia. Indeed, colonization with candida has been recognized as an important risk factor for hospital candidaemia. Importantly, colonization by identical Candida strains preceded candidaemia in all studies that addressed the issue. In an attempt to quantify candida colonization in a surgical ICU population, Pittet et al. introduced the colonization index (CI) defined as the ratio of colonized body sites over the total number of body sites screened. A cut-off value of 0.5 had a sensitivity of 100% but a low positive predictive value of 66% in identifying surgical patients with systemic candidiasis. However, after correction for the heavily colonized sites, the positive predictive value increased to almost 100% while maintaining the same sensitivity. These and other data indicate that the higher the density of colonization the higher the risk of subsequent development of candidaemia. It appears as
though patients who are colonized upon admission to ICUs are more likely to later develop a CI >0.5. This stresses the importance of candida screening for all patients at least upon entry to ICUs. Other underlying diseases and conditions associated with heavy colonization (CI >0.5) are haematological malignancies, prolonged treatment with broad-spectrum antibiotics and candiduria. Interestingly, medical ICU patients are more frequently densely colonized upon onset of candidaemia compared to those in surgical ICUs.34

Candiduria in ICUs: incidence, risk factors and mortality

The incidence of candiduria in the ICU population is increasing and currently ranges from 19 to 44% of urine specimens depending upon patient cohort and definition of candiduria.35–37 It should be noted that neither the presence of symptoms and signs of urinary tract infection, nor the colony counts in the urine are helpful in the interpretation of the clinical importance of candiduria.38

Most ICU studies consider a urine culture positive for candida when there are ≥10³ cfu/ml, whereas heavy candiduria is defined as ≥10⁴ cfu/ml. The commonest species (>45% of cases) is C. albicans, with C. glabrata being the second.35,37,39 The most important predisposing factor is catheterization of the bladder. Additional risk factors identified in ICU patients include prior use of antibiotics, female sex, age over 65 years, extended hospital stay before ICU admission, diabetes, TPN and mechanical ventilation.35,37

Detection of candiduria is associated with an approximately threefold increase in the probability of death in the ICU after adjusting for other covariates associated with mortality, such as length of ICU stay, age and treatment with antibiotics.40 The overall mortality associated with ICU candiduria can reach 50%.35,41

Candiduria as a marker of heavy colonization

Approximately 50% of patients with candiduria are simultaneously colonized at other body sites.42 Candiduria is positively correlated with heavy colonization and a CI >0.5.32,43 The heavier the candiduria, the stronger this correlation becomes. A prospective study in 15 French ICUs showed that 65% of patients with heavy candiduria (cfu >10⁴) also had a CI >0.5 as opposed to 31% of those with fewer urine colony counts.44 The same results were reproduced by another French study involving a mixed medical and surgical ICU population.42 Furthermore, candiduria seems to correlate with invasive disease significantly more than colonization of other body sites, whereas absence of candida in the urine has a nearly 100% negative predictive value for systemic infection.40

These data raise the question whether candiduria can potentially be used as a marker of dense colonization in place of the CI. Although such use of candiduria needs to be confirmed by additional data, it might prove to be a more practical test than calculation of CI, which generally requires extensive human and laboratory resources and significant increase in work load and costs.43

Association between candiduria and candidaemia

Most studies on prevalence of candiduria in patients with nosocomial candidaemia involve a non-ICU population. In this setting, a definite urinary source is identified in only 10% of patients with candidaemia, and urinary tract obstruction related to malignancies is the commonest risk factor for dissemination of a urinary tract candida infection.45,46

In patient cohorts consisting exclusively of critically ill patients, candiduria is significantly associated with candidaemia and its incidence ranges from 46 to 68% of candidaemic patients.10,35 Independent risk factors associated with candidaemia in the presence of candiduria are urgent surgery, extrarenal depuration procedures and parenteral nutrition.

Importantly, in all relevant studies candiduria was detected prior to development of candidaemia indicating a probable ascending route of infection. Indeed, candida genomic material has been detected in the serum of 40% of critically ill patients with persistent candiduria.47 When sophisticated strain identification techniques are used, identical genotypic patterns of strains isolated from blood and urine are found in most cases.30,48–50 Strain variability could be explained on the basis of strain microevolution.51 In recent years it has become evident that Candida produce genetic variants rapidly and that this capability is at the core of their success as commensal and opportunistic pathogens.52 Indeed, such a strain microevolution has been noted in cases of recurrent or persistent candidaemia.53
Treatment of candiduria

There is accumulating evidence suggesting that candiduria is a marker of heavy colonization and can be associated with disseminated infection. Nevertheless, it is still unclear whether all ICU patients with candiduria should be pre-emptively treated with antifungals. A number of authors have attempted to define a group of ICU patients at high risk for invasive candidiasis. Papithou et al. proposed a prediction rule based on a retrospective study on surgical ICU patients who stayed in the ICU for more than 48 h. They found that any combination of diabetes mellitus, new-onset haemodialysis, use of broad spectrum antibiotics and use of TPN could identify cases of disseminated infection.

We believe that a predictive rule that does not take into consideration the extent of colonization may not be very useful. In fact, in the absence of colonization, disseminated candidiasis is unlikely regardless of the presence of predisposing factors. For this reason, every attempt to quantify risk for candidiasis in ICU should incorporate a measure of colonization. This was the approach taken by Leon et al., who used data from the EPCAN project, a prospective multicentre study of candidal infection and colonization in ICU patients. After adjusting for possible confounding variables they concluded in four factors independently associated with proven systemic candida infection: surgery on admission, TPN, severe sepsis and multifocal colonization. They devised a 'Candida score' by assigning a weight of 1 in each of TPN, surgery and colonization and a weight of 2 for severe sepsis. A combination of sepsis with any of the other risk factors or all three other factors together except for sepsis gave a Candida score of 2.5, which had a sensitivity of 81% and a specificity of 74% to detect systemic candidiasis. The validity of the proposed Candida score needs to be further tested. Also it remains to be answered whether candiduria can be used instead of multifocal colonization for the calculation of this or similar scores.

From information currently available it is not unreasonable to consider therapeutic intervention in a critically ill patient who presents with heavy candidal colonization and concurrent clinical risk factors predisposing to dissemination. In this setting, candiduria could be used as a marker of colonization and replace the use of surveillance cultures, which are more cumbersome and costly. The therapeutic approach to persistent candiduria depends primarily on the clinical picture. Unexplained fever or signs and symptoms of ongoing unidentified infection may warrant systemic antifungal agents in the form of either fluconazole or intravenous amphotericin, if fluconazole has been used previously or if the prevalence of non-albicans Candida is high in the treating institution.

In the absence of sepsis, candiduria should not be ignored in the critically ill. In this setting, elimination or, at least, change of the urinary catheter should be attempted first. The coexistence of various risk factors for candidaemia may prompt prophylaxis. Use of fluconazole has been shown to prevent invasive candidiasis in bone marrow, liver transplant, surgical patients with anastomotic leaks or recurrent gastrointestinal perforations and in critically ill patients in combination with selective digestive decontamination.

A common characteristic of such patients is the high degree of candida colonization although there are no data on the particular incidence of candiduria.

The decision to proceed with prophylaxis should, as always, be based on the whole clinical picture of which candiduria is one part, however important. If fluconazole is selected for prophylaxis, intravenous administration might be preferable since the impaired digestive function of critically ill patients might impair absorption. Amphotericin bladder washes are potentially useful in temporarily decreasing candida urine burden although their therapeutic value is being questioned.

Conclusion

Modern ICU technology in conjunction with an increasing population of critically ill patients has substantially increased the incidence of candiduria. Current evidence suggests that there is a link between candiduria and heavy colonization, therefore making candiduria a risk factor for invasive candidiasis. Through its association with candidaemia, candiduria in ICUs has a mortality that may exceed 50%. In view of this high mortality, every effort should be made to identify ICU candiduria and evaluate it in connection with other risk factors for systemic candidiasis. Treatment decisions should be based on individual patient data.

References

Candiduria in ICUs


