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Management of Candiduria: Grey Zones Still Exist

Candida species cause a wide spectrum of diseases, of which the prevalence of candiduria varies considerably between nosocomial settings, being most prevalent among patients admitted to the intensive care unit (ICU). However, lacking management and treatment guidelines and the existence of dilemmas have inhibited efforts to curtail cases of candiduria for this vulnerable population.

Critically ill patients are a susceptible group for opportunistic *Candida* infections. The major risk factors identified with candiduria are extremes of age, female sex, diabetes mellitus, use of immunosuppressive agents, interruption of the flow of urine, radiation therapy, and so on. However, in nosocomial settings, the major risk factors are the use of urinary catheters and the prior use of broad-spectrum antimicrobial agents (Passos et al. 2005).

Presently, the incidence of candiduria in the ICU population ranges from 19% to 44% of urine specimens, depending upon the patient cohort and the definition of candiduria (Toya et al. 2007). The causative species of candiduria vary in different studies. *Candida albicans* is responsible for at least 50% of all cases of funguria, followed by *Candida glabrata* (15.6%), *Candida tropicalis* (7.9%), *Candida parapsilosis* (4.1%), and *Candida krusei* (1%) (Kauffman et al. 2000). *C. glabrata* most often is isolated from individuals who have been treated with fluconazole, while *C. parapsilosis* is seen most frequently in neonates. It is noteworthy that for approximately 10% of patients with candiduria, at least two types of *Candida* species are isolated from the same urine culture. Candiduria frequently coexists with or follows bacteriuria.

Treatment Dilemmas

The major problem with candiduria is in determining its practical importance. The condition can arise as a result of contamination, colonisation or a true urinary tract infection. Due to lack of a reliable method for differentiating colonisation from infection, the condition is a dilemma for the clinician from the treatment point of view. Frequently it has been reported to be the first sign of disseminated disease or candidaemia. After adjusting the various covariates, the overall ICU mortality rate among patients with candiduria has been found to reach 20-50% (Hollenbach 2008). Therefore, if neglected, it can evidently be detrimental for the patient. As a result, even if the decision is not to treat the patient, the clinician has to be vigilant. In the case of isolation of *C. albicans*, the possibility of colonisation should be kept higher than true infection as it is a part of normal flora, especially in female patients. However, if non-*albicans Candida* are isolated, it is advisable to determine whether it is really colonisation. There is also need to perform surveillance cultures at various body sites of the same patient to determine the colonisation index.

As far as the question of when to start the treatment cutoff is concerned, there are no clear-cut guidelines. The decision lies upon the clinical acumen of the attending physician. Asymptomatic candiduria is usually expected to resolve within weeks to months without therapeutic intervention in the vast majority of individuals. Treatment is warranted only in certain patient populations, such as those at risk for developing a disseminated fungal infection. These include neutropenic or oncology patients, patients with sepsis, infants with low birth weight, neonates, those with a known urologic obstruction and those likely to undergo urologic manipulations (Lundstrom et al. 2008). In cases of asymptomatic candiduria in outpatients or other predisposed inpatients, the best method is to get rid of predisposing conditions. However, in ICU patients, it may not be possible to remove the catheter permanently, stop the ongoing antibiotic therapy or make the patient undergo surgery for predisposing urologic abnormality immediately. In such conditions, careful monitoring is required. The patient's urine cultures should repeatedly be tested for *Candida* so that if presence is detected the possibility of contamination can be ruled out. The Microbiology laboratories cannot help much in differentiating colonisation from infection on their own. The cutoff value for candiduria that indicates presence of infection varies from 103 to 105 colony-forming units (CFUs) The problem of multiple species in the same sample, and cutoff criteria for cases of non-*albicans Candida* species isolation, are still to be addressed. There have been some attempts to distinguish infection from colonisation of the bladder by looking for the presence of pseudohyphae or antibody-coated yeasts in the urine. However, species such as *C. Glabrata* do not produce pseudohyphae, and *C. albicans* can be induced to form pseudohyphae by varying the pH and nutrients in the urine. Detection of antibody-coated yeast has also been shown to be non-specific (Hollenbach, 2008).

For the symptomatic conditions like pyelonephritis and fungus ball, clear-cut treatment guidelines have already been defined (Pappas et al. 2009). Even in cystitis, the patient is usually symptomatic and fluconazole is given as a first line of treatment. In cases of fluconazole resistant species, the treatment is amphotericin B (deoxycholate, as liposomal amphotericin B achieves low concentration in renal tissue) or flucytosine. However, fluconazole use is limited in the context of advanced renal failure and infections with non-*albicans* species, most notably *C. glabrata*. Echinocandins are usually recommended in invasive or disseminated candidiasis, but in renal involvement their efficacy is not proven, due to their poor urinary bioavailability. Some authors have found that candiduria was eradicated in their patients after parenteral caspofungin therapy was given (Sobel et al. 2007). Parenteral caspofungin achieved high renal tissue concentrations independent of glomerular filtration. Currently, IDSA guidelines do not recommend echinocandins for treatment of candiduria because of very limited clinical data. The feasibility of caspofungin administration via a nephrostomy tube also needs to be determined. It is still to be seen whether the potent activity of caspofungin against *C. glabrata* (a frequent uropathogen) and other non *albicans Candida* can be exploited or not (Sobel et al. 2007).

Last but not the least, the presence of yeast cells in urine is labelled as candiduria traditionally; but now many new fungi like *Trichosporon* species are emerging as frequent isolates in urine samples of hospitalized patients (Singla et al. 2012). The existing data also reveals a profile of

high resistance of the genus *Trichosporon* to amphotericin B and itraconazole with moderate resistance to 5- flucytosine (Sun et al. 2012).

Management and Guidance

Due to increasing *Candida* infections, an increase in non-*albicans Candida* and other yeast, increasingly compromised immune systems increasing predisposition to *Candida* and *Candida* establishing itself at position four in the isolation list from bloodstream infections, we can no longer neglect *Candida*'s isolation from body sites, even from a urine sample. There is a need to establish a *Candida* surveillance programme for all ICU patients and to follow-up patients with candiduria even after their discharge from an intensive care facility, to generate authentic data regarding its pathogenicity. Guidelines available do not dwell much on cutoff definitions and culture techniques to be employed. Various studies have kept their own criteria for analysis of candiduria. Some studies even show gender bias (Achkar et al. 2010). This variability and unreliability in laboratory procedures skews the analysis of the incidence and outcome of candiduria. Most of the studies have concentrated on epidemiology and risk factor evaluation, but it is also important to have data on recurrences and relapses, with uniform definitions for these terms, after treatment has been given. *Candida*, being a master in opportunism, exhibits strain microevolution and genetic variability. This fact has been supported in cases of candidaemia (Toya et al. 2007). Similar reasons could be there for persistence and relapse in cases of candiduria too. Lack of consensus and the availability of limited literature are the main reasons that we cannot formulate the proper guidelines. For the time being, the approach to candiduria remains individualised and proper assessment of the patient's risk factors is the key to treatment.

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