Invasive Candidiasis: Turning Risk into a Practical Prevention Policy?

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See the article by Blumberg et al. on pages 177–86.

For 3 decades, systemic antifungal use was virtually a 1-drug act—amphotericin B. Administration of antifungal agents to critically ill patients was dominated by fear of toxicity rather than knowledge of its efficacy. In the past decade, the availability of azole antifungal agents with enhanced pharmacokinetic and safety profiles completely revolutionized systemic antifungal use. If anything, their arrival caught clinicians unprepared, and guidelines for the optimal use of triazoles lagged behind common practice utilization. Use of azole drugs in the surgical intensive care unit (SICU) has become an established fact of life, with use unimpeded by the slow development or, in many areas, complete absence of useful data.

In the meantime, the frequency of invasive, often life-threatening candidal infections has increased dramatically [1, 2], largely as a function of medical technological advances (e.g., vascular catheters, total parenteral nutrition [TPN], hemodialysis) and the enhanced ability of clinicians to keep critically ill patients alive. Much early attention was focused on patients with neutropenia, and considerable progress has been made in validating the efficacy of antifungal prophylaxis and conducting prospective, randomized, controlled trials that support the use of antifungal agents for the treatment of persistently febrile patients with neutropenia who do not respond to antibiotics [3, 4]. These 2 policies have resulted in control of and actual reduction in the frequency of bloodstream infections (BSIs) due to Candida species and systemic candidiasis in patients with neutropenia.

Now attention has turned toward patients without neutropenia. In fact, most BSIs due to Candida species now occur in patients who have been hospitalized in intensive care units (ICUs), especially adult SICUs and neonatal ICUs. Moreover, throughout the world, the dominance of Candida albicans has been challenged by the increased prevalence of serious infection caused by non-albicans Candida species. Candida species are now the fourth most common bloodstream isolates, following coagulase-negative staphylococci, Staphylococcus aureus, and enterococci [5–7]. Although BSIs caused by Candida species continue to be the primary end point in observational and interventional studies, invasive candidal infections that involve the abdominal cavity, bone, soft tissue, or other sites are no less important and are responsible for considerable morbidity and death.

Several retrospective studies have identified multiple risk factors for candidal BSI in patients in the ICU [8–14]. Most of the risk factors have been repeatedly verified, although others are more controversial. Major risk factors include use of central venous catheters, TPN, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization. In addition to these data, we now have the findings of Blumberg et al. [15] from a detailed prospective evaluation of risk factors for candidal BSI, performed under the auspices of the National Epidemiology of Mycoses Survey (NEMIS).

In the NEMIS study [15], data were collected prospectively from 6 SICUs in the United States. Forty-two BSIs in 4276 patients were identified during a 2-year period. Once again, the dominant risk factors were prior surgery (RR, 7.3), acute renal failure (RR, 4.2), and TPN (RR, 3.6), with a significant trend toward candidal BSI developing in association with shock, disseminated intravascular coagulation, and adult respiratory distress syndrome. Other important findings included the contributory role of the triple-lumen catheter in surgical patients.

A key additional analysis demonstrated...
that not all patients in the SICU are at equal risk of invasive candidiasis. Of note, patients who undergo neurosurgical or ear, nose, and throat procedures appear to be at the lowest risk, followed by orthopaedic and gynecologic patients. As multiple previous studies have shown, abdominal surgery proved to be the highest risk. Neither corticosteroid use, a controversial risk factor for candidemia, nor severity of illness (as measured by acute physiology and chronic health evaluation II scores [16]) emerged as a contributory factor in the study.

Even more interesting is that colonization with *Candida* species was also not found to be an independent risk factor for candidal BSI. In the NEMIS study, weekly rectal and urinary surveillance cultures were performed. The positive predictive value of colonization was <3%. The latter observation is in contrast to the findings of several previous studies in which colonization was linked to risk of candidemia [8–10]. The cause of this difference may be the design of the studies. Wey et al. [8] and Bross et al. [9] used a case-control design, whereas Pittet et al. [10] studied relative degrees of colonization among a highly selected group of at-risk patients. The NEMIS study, on the other hand, included a very large control group of all other contemporaneous patients in the ICU, many of whom were at only minimal risk for invasive candidiasis because of relative youth, brevity of ICU stay, or similar factors. Therefore, the strength of colonization as a risk factor may have been less than that of factors that predispose to colonization and subsequent infection. Barring direct inoculation, colonization is presumably a near-absolute requirement for infection, and the strength of the data suggesting the relevance of extent and density of colonization is difficult to deny.

What did we learn from the NEMIS study with regard to pathogenesis of candidal BSI in patients in the ICU? Very little, in that no new risk factors emerged and no understanding of pathogenic mechanism was possible. It is simplistic to assume that only 1 pathogenic mechanism would be operative. The portal of entry in some patients is transversely via intravascular catheters, especially triple-lumen catheters, facilitated by frequent use, TPN, and the potential for contamination of catheters by medical staff who are colonized with *Candida* species. In other patients, primary pathology, such as peritonitis, bowel ischemia or manipulation, leads to cases of candidemia that are unrelated to catheter presence.

How, then, do acute renal failure, hemodialysis, shock, disseminated intravascular coagulation, and adult respiratory distress syndrome contribute to invasive candidiasis? Is enhanced colonization, an increased number of intravenous lines, prolonged exposure, or an increased amount of intensive nursing responsible, or do host resistance factors enter the equation? In addition, what is the mechanism whereby use of multiple antibiotics predisposes a patient to candidemia? The concept that the gut is the true primary source for most cases of disseminated candidiasis might serve to tie these ideas together. *Candida* species have been shown to be able to traverse the normal gut epithelium [17], and detailed work involving patients with leukemia has shown that relative degrees of increase in gut permeability (measured by changes in absorption of α-xylose) are linked to the frequency of neutropenic enterocolitis and hepatosplenic candidiasis [18]. In fact, it has been speculated that most bacterial infections in patients with neutropenia arise from the gut [19–21]. Might a similar process not be operative in at least some patients without neutropenia? The reduction in the bulk of competing microorganisms by broad-spectrum antimicrobial agents, especially those that affect the anaerobic flora of the gut, would be a logical explanation.

The most important contribution of the NEMIS observational study is to highlight the potential protective role of antifungal agents in reducing the risk of candidal BSI. The role of antifungal prophylaxis in the SICU remains extremely controversial [22–24]. Whether antifungal agents were used as prophylaxis or empirical therapy for fever, Blumberg et al. [15] were able to detect sufficient clinical use to detect an impact on patients with candidiasis. The authors emphasize the need for prospective, randomized trials to confirm the protective role of antifungal prophylaxis. At least 5 studies that have evaluated prophylaxis have already been reported, and they yielded mixed results [14, 25–28]. Unfortunately, the studies that failed to show any benefit of prophylaxis were doomed *ab initio* because of the lack of power to show benefit and the inclusion of low-risk patients in the SICU.

On the other hand, those studies that did show benefit did so either by using highly selective criteria [14] or by studying patients in an unusually high-risk ICU setting [28]. The NEMIS study reinforces the concept that although the SICU is the epicenter of the invasive candidiasis epidemic, the majority of such patients are at low risk, with an overall 1% incidence of BSI due to *Candida* species. The subpopulations at highest risk include patients who undergo liver transplantation [29–32], (possibly) patients who undergo pancreas transplantation [33], and patients with persistent or refractory gastrointestinal leakage [14]. The work of Blumberg et al. [15] suggests that we might add to this list critically ill postoperative patients, especially but not exclusively after they undergo abdominal surgery, in association with acute renal failure and the obligatory appendages of intravascular triple-lumen catheters.

Nevertheless, we need additional meaningful stratification of identified risk factors, because far too many surgical patients who have catheters and who are receiving antibiotics develop mild acute renal failure and require ventilatory support. The finding in the NEMIS study that colonization measurement did help select the highest-risk patients is disapp
pointing, because so many other studies have shown this association. On the other hand, the thought of performing expensive, routine surveillance cultures to identify at-risk patients is terrifying. What is needed is specific guidance regarding the site(s) that should be cultured, at which point during a patient’s at-risk period they should be cultured, and whether density of colonization should be routinely determined.

Have we done enough to identify those high-risk surgical patients who will benefit from antifungal prophylaxis without exposing thousands of lower-risk patients to expensive antifungal therapy? The NEMIS study suggests that we have not and illustrates that potential for widespread prophylaxis use will select for less-susceptible non-albicans Candida species and induce azole-class resistance. The NEMIS study sets the stage for large, prospective, multicenter, randomized interventional studies of antifungal prophylaxis in which high-risk (but not all) surgical patients can be enrolled. Until then, antifungal prophylaxis should be used only for very select high-risk patients, including a very small proportion of patients in the SICU.

References
