Editorial

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Yeast Infection in Immunocompetent Patients: Fomenting Ferment to Foil the Fermenter

Interest in candida species as a cause of hospital-associated infection is currently outstripped only by the recent focus on coagulase-negative staphylococci as significant nosocomial pathogens. Once considered little more than saprophytic nuisances, *Candida sp.* have assumed a progressively important role as hospital-associated pathogens. Coincident with the advent of effective, broad-spectrum antibacterial therapy, *Candida sp.* have become more commonly isolated from clinical specimens, not only in tertiary referral centers where severely immunocompromised patients are often treated, but also in acute care and community hospitals. In one major municipal hospital *Candida sp.* are the fifth most common blood culture isolate.[1] In 1984, candida was the fourth most common blood culture isolate at The Clinical Center of the National Institutes of Health, trailing only *S. epidermidis*, *S. aureus*, and *E. coli* (VJ Gill, personal communication). Clinically significant candidal syndromes such as candida endophthalmitis,[2] candida osteomyelitis,[3] candida meningitis,[4] candida peritonitis,[5] and, most recently, candida hepatitis[6] have become relatively commonplace. Whereas, *Candida sp.* have become well-recognized as opportunistic pathogens in febrile, granulocytopenic cancer patients, the role of candida as a nosocomial pathogen in the acute-care hospital has been less frequently stressed. Traditionally, candida infections have been associated with a number of underlying illnesses, particularly hematologic and reticuloendothelial malignancies, and patients with so-called "solid" tumors who are receiving immunosuppressive chemotherapy. More recently, literature is emerging which emphasizes candida as an all-too-often unrecognized pathogen in immunocompetent patients. Often such patients have sustained traumatic injuries, such as penetrating abdominal wounds or motor vehicle accidents. Just as frequently, patients develop deeply invasive candidiasis as a complication of major abdominal surgical procedures. Although immunocompetent, such patients are often seriously ill. Careful studies have identified a number of factors—most of which are iatrogenic—which are associated with or predispose the patient to the development of deeply invasive candidiasis. Such seriously ill patients require frequent and often prolonged courses of broad-spectrum antibacterial agents. Whereas these drugs are needed to combat intra-abdominal infection, they also suppress the normal cutaneous and gastrointestinal microflora, thus opening the door to candidal proliferation. Some investigators have also suggested that certain antimicrobial agents, in particular sulfonamides,

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tetracyclines, and aminoglycosides, may have negative effects on granulocytes—the cell line that appears to be one of the most, if not the most, important lines of anti-candida defense.[7]

Additionally, many of the diagnostic procedures and therapeutic modalities commonly used in these patients may contribute to an increased risk for deeply invasive candidiasis in the seriously ill immunocompetent patient. The use of total parenteral nutrition (TPN) has long been associated with an increased risk for deeply invasive candidiasis.[8] Other proposed risk factors (eg, central venous catheters, flow-directed, balloon-tipped pulmonary artery catheters, arterial pressure-monitoring devices) have been less well-documented as clear risk factors for candida infection. Such devices do, however, provide an easy portal of entry for the cutaneous microflora surrounding the skin-entry site. Thus, almost insidiously, candida infections have become an important cause of morbidity and mortality in postoperative patients. In one study, Solomkin and co-workers emphasized the necessity of antifungal chemotherapy for patients developing candidemia following complications of intra-abdominal surgery.[9] In their study, 31 of 36 patients who were not treated for candidemia died.

In this issue, Walsh and co-workers report *Candida sp.* as a significant cause of peripheral intravenous catheter-associated suppurative thrombophlebitis in an acute-care hospital.[10] The authors performed a retrospective analysis and identified seven patients who met their case definition for this syndrome. Although their report suffers some of the ailments common to virtually all such retrospective studies, it serves to emphasize the role of these yeasts as causes of significant, life-threatening intravascular infections in patients whose immune systems are reasonably intact. As in other studies, Walsh et al found a clear association between prior antibiotic use and the development of suppurative thrombophlebitis caused by candida. The retrospective nature of their interesting report, however, precluded their being able to assess several important issues regarding the epidemiology and pathogenesis of these infections. Although the associations cited above between clinical procedures, therapeutic modalities, and underlying illnesses that result in an increased risk for acquiring deeply invasive candidiasis are well-established, the precise pathogenic mechanisms which contribute to this increased risk are poorly understood. Among the important issues which need to be addressed regarding the epidemiology and pathogenesis of nosocomial candidiasis are the following:

1. What are the effects of various therapeutic interventions (eg, topical antiseptics, semi-permeable membrane dressings, systemic administration of antifungal agents) on the ecology of candida on the skin? Do specific bacterial organisms inhibit or impair local yeast proliferation such as is apparently the case with some strains of *S. epidermidis* that inhibit cutaneous colonization with certain Enterobacteriaceae?[11]
2. Are there variations in pathogenicity of candida isolates that correlate with difference in adherence of candida to epithelial or perhaps endothelial cells?
3. Does the chemical composition of an intravascular device affect the risk of subsequent candida adherence, colonization, and intravascular invasion?

Although most of these issues are difficult to assess in the clinical setting, several investigators are beginning to address these and other issues relevant to the pathogenesis of nosocomial candidiasis.

The issue of local care of catheter sites remains controversial. A number of studies have suggested a limited effect of applying antimicrobial or antiseptic ointment over the insertion site. To my knowledge, no study has conclusively demonstrated the efficacy of these substances in preventing catheter-associated infection. Conversely, some investigators have suggested that antibiotic ointments (containing no anti-fungal agents) may actually increase the risk for *Candida sp.* colonization and/or infection. Additional studies have suggested that semi-permeable dressing materials may provide an environment under the dressing which actually fosters microbial growth.

Further clarification of the relative importance of the resident flora, antibiotic or antiseptic ointments, dressing materials and other commonly used therapeutic interventions to the prevention of catheter-associated candida infection could have broad implications for the care of patients, both in terms of the decreased morbidity and mortality, as well as the possibility of decreased cost, should some of the commonly used interventions prove ineffective or detrimental. Clearly, this is an area where careful studies may be valuable to the infection control community. In any event, it is clear that many iatrogenic interventions result in an increased risk for cutaneous candida colonization, even in the face of relatively intact host defenses.

Although we are now beginning to understand factors associated with an increased risk for cutaneous candidal colonization, little is known regarding the mechanisms used by the yeast to invade the vasculature. For example, until recently, little was known regarding the ability of these yeasts to adhere to human cells. In careful studies *Candida sp.* have been shown to adhere actively to human buccal[12] and vaginal[13] epithelial cells. Further studies have suggested that growing candida in the presence of sucrose increases their ability to adhere to epithelial cells. Lee and King have suggested that the adherence of candida to epithelial cells is mediated by a fibrillar polysaccharide on the surface of the yeast.[14] Indirect evidence suggests that candidal mannan, mannoproteins, and perhaps chitin may be important constituents in the adherence of candida to epithelial cells.

Additional studies have examined the mechanisms of adherence of candida to cardiac vegetations (ie, fibrin-platelet matrices), to heart valves, and, perhaps most interestingly, to vascular endothelial cells. In elaborate studies, Calderone and co-workers have demonstrated that candida yeasts readily adhere and rapidly contribute to the expanding mass of experimental endocardial vegetations, in part due to candida-platelet interactions.[15] Again, a mannoprotein has been implicated as an important participant in the adherence of candida to fibrin-platelet matrices.[16] The human cell receptor which mediates the attachment to fibrin-platelet clots is unknown; however,

some investigators have hypothesized that fibronectin, an important cell-surface glycoprotein, may be the receptor.[17] More recently, investigators have demonstrated that *Candida sp.* actively adhere to and invade human endothelial cells, both in vitro and in vivo. Although candida mannan again appears to play at least a contributory role in the adherence of candida to endothelial cells,[18] most preliminary studies suggest that the mechanism or mechanisms for candidal attachment to endothelial cells appear to be different from attachment mechanisms for other human cell systems.[19] Edwards and co-workers have recently demonstrated that candida hyphal and pseudohyphal elements express receptors for and actively bind degradation products of certain human complement components in a fashion similar to binding by human inflammatory cells.[20] These studies raise the intriguing possibility that the candida-complement interaction may play a role in the adherence to and invasion of human cell surfaces. Thus this yeast, once thought to be a saprophytic bystander, may have sophisticated techniques for defending (or perhaps at least camouflaging) itself as a pathogen—even in immunocompetent patients.

Another relevant area where studies are just beginning is that of candidal adherence to plastic surfaces, for example to the substances used in the manufacture of devices which are placed into the vascular system. In one laboratory study, candida were demonstrated to adhere more aggressively to polyvinylchloride catheters than to catheters made of teflon®.[21] Extension of these studies to include assessment of other factors in the intravascular environment (eg, fibrin, platelets, fibronectin, etc.) would appear to be both prudent and promising. Thus, both yeast-based and host-based factors appear to be playing a role in the pathogenesis of candida infection in immunocompetent patients.

The report by Walsh and colleagues in this issue of *Infection Control* of several cases of suppurative thrombophlebitis caused by *Candida sp.* is interesting for several reasons. First, it calls attention to candida as a significant pathogen in patients who are not immunosuppressed, and in a setting in which candida has not been commonly seen as a pathogen. Secondly, their report emphasizes what we currently know about the pathogenesis of candida infection (ie, the role of broad-spectrum antibiotics in increasing the risk for both colonization and infection with candida). Third, their retrospective study emphasizes the need for further careful scientific studies designed to delineate what we currently do not know about the pathogenesis of candida infection in immunocompetent patients—(ie, the factors responsible for adherence, colonization, and invasion of both the colonized cell and of the intravascular space). Finally, their study suggests, but by no means proves, that inadequate local catheter care may have contributed to the increased risk of candidal suppurative thrombophlebitis. When possible, rotation of intravenous access sites seems advisable; and, when this is not practical, careful observation of the catheter insertion site seems prudent. The roles of antiseptic ointments, semipermeable dressings, in-line membrane filters, routine intravenous site care, and other techniques in the prevention of catheter-associated septic complications remain controversial.[22] The report by Walsh and co-workers again emphasizes the need for large, carefully controlled studies to assess the efficacy of such therapeutic modalities in preventing catheter-associated sepsis.

The spectrum of nosocomial candidiasis is continuing to change. Initially considered a nonpathogenic saprophyte, then an opportunistic invader of severely immunocompromised patients, *Candida sp.* are now recognized as important pathogens in immunocompetent patients, particularly in complicated surgical patients and patients whose therapy requires long-term placement of intravascular devices. Studies of skin ecology, colonization, adherence, attachment, and invasion by candida will hopefully lead to innovative techniques that can prevent iatrogenic candidiasis by interrupting mechanisms essential to the pathogenesis of these often devastating infections.

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