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EDITORIAL

Darwinian competition and the pathogenesis of opportunistic infection in the transplant recipient*

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In recent years there has been an exponential increase in the number of patients that can be characterized as immunocompromised. A significant part of this increase is caused by the HIV/AIDS epidemic; equally important is what we have termed the 'quiet revolution' – an ever increasing population of patients who, in past decades, rapidly succumbed to their end-stage organ dysfunction (e.g., kidney, heart, liver, and lung failure) or their systemic disease (e.g., systemic lupus, leukemia, cancer, or congenital immunodeficiency). Today, because of advances in the care of their underlying conditions, particularly with transplantation, these individuals have the potential of being rehabilitated and restored to normal life. No longer are they at immediate risk from their original disease; rather, they are at risk for complicating infection, made possible by the host defense deficits that have occurred as a result of their underlying disease and/or its treatment. Although these compromised hosts remain at risk for the same processes that affect the normal population (e.g., influenza, gram-positive skin and soft tissue infection, urinary tract infection, etc.) a new element has been added – the occurrence of opportunistic infection [1].

The incidence of infection, particularly opportunistic infection, in the compromised host is primarily the result of the interaction of four factors: (i) technical/anatomic abnormalities that compromise the protective effect of the intact mucocutaneous surfaces, and/or result in devitalized tissue, or an undrained fluid collection; (ii) environmental exposures to contaminated air and/or potable water; (iii) the presence of factors that confer a Darwinian advantage to one or more microbes; and (iv) a complex function termed the net state of immunosuppression. The present case of peritonitis with *Fusarium* species in a transplant patient illustrates the interaction of these factors [1–4].

The technical/anatomic abnormalities of importance in the compromised host fall into several categories: a surgical misadventure; skin injury, including those due to burns, trauma, water immersion injury, eczema, etc.; the requirement for drainage tubes of various types that not only bypass the skin, but also are more directly associated with infection (e.g., vascular access catheters); and the causation of devitalized tissue and/or fluid collection. The technical requirements for immunocompromised patients are

particularly demanding, requiring technically perfect surgery and the appropriate management of vascular access [5].

Immunocompromised patients have traditionally been regarded as 'sentinel chickens' who are the first to demonstrate the effects of an excessive environmental hazard, whether that be in the community or, more commonly, in the hospital [6]. Thus, occurrence of the life-threatening *Legionella*, vancomycin-resistant enterococcal infection, and such fungi as *Aspergillus*, *Cryptococcus*, *Candidia*, as well as the so-called 'newly emerging fungi' (which now account for >10% of opportunistic fungal infection) is a particular problem for these patients. There are a variety of these newly emerging fungi (e.g., *Fusarium*, *Scedosporium*, *Penicillium* and *Mucor*) that share a number of characteristics in common: they are saprophytes in the soil, plant pathogens, and are common in the environment; direct inoculation into the skin or inhalation are the common mechanisms of entry; bloodstream infection is common, with *Fusarium* being isolated from the blood in as many as 50% of cases. Like invasive aspergillosis, *Fusarium* is frequently angioinvasive, accounting for the three cardinal findings: hemorrhage, infarction, and metastases. These organisms tend to adhere to catheters, vascular access devices, chronic ambulatory peritoneal dialysis catheters, as well as contact lenses. Disease can be because of the direct invasion of such tissues as the lung and skin or the result of the production of mycotoxins. Defects in neutrophils and cell-mediated immunity are important factors in the pathogenesis of these infections. Common presenting clinical syndromes include hepatosplenic disease (akin to hepatosplenic candidiasis), skin lesions and/or lung nodules, as well as manifestations of hematogenous disease [7,8].

In this case a peritoneal infection was being evaluated at the time the transplantation surgery occurred. Subsequently, *Fusarium* was isolated from cultures taken pretransplant. Proceeding with a transplantation procedure in the setting of a poorly defined infection must be performed with great care. Once the *Fusarium* infection was recognized, the possibility of amphotericin, caspofungin, fluconazole, and itraconazole resistance was investigated, and cure was effected by voriconazole. As a general rule, identification of a process being caused by one of these emerging mycoses should lead immediately to antifungal susceptibility testing for the possibility of infection resistant to such standard drugs as amphotericin and fluconazole. In this situation, voriconazole should be initiated immediately, with the substitution of other drugs contemplated only after antifungal sensitivity testing is completed.

As expected, this patient's net state of immunosuppression was clearly high after transplantation, given his immunosuppressive regimen (antithymocyte therapy plus tacrilimus, mycophenolate, and prednisone), recent surgery and the coexistence of cytomegalovirus infection. When possible pre-existing infections should be cured prior to the transplant procedure [1–4].

An important part of the care of immunosuppressed patients is to recognize the role of Darwinian selection in the pathogenesis of a particular infection. Although in bone marrow and leukemic patients, it is said that a major source of infection is the endogenous flora, it is estimated that ≥50% of the organisms causing infection in the patient include antimicrobial resistant species of bacteria and/or fungi [1–5]. Previous antimicrobial therapy will both eradicate normal flora and select for resistant organisms as the prior anti-microbial therapy (e.g., Fluconazole) may have done in this case [9]. In addition, specific problems develop: attempts to chelate iron overload syndromes will markedly increase the risk of mucormycosis, as will acidosis; attempts to provide prophylaxis against a variety of potential pathogens will select for increasing resistance, whether the organism is gram-negative, gram-positive or fungal.

In addition to metabolic and antimicrobial pressures, the health of the patient has a significant effect on the patient's normal flora. For example, the normal flora in the orophyarnx is maintained by specific ligand-receptor interactions; that is, specific adhesins on oral streptococcal species interact with specific receptors on the oral mucosa. Such interactions provide a powerful advantage to maintaining the normal flora as nonvirulent, gram-positive and antibiotic susceptible. In the face of disease, metabolic disarray, smoking, cancer, many drugs, etc., this advantage is lost and overgrowth with potential pathogens will result, particularly if antimicrobial pressures are combined with these events.

In sum, an ecologic niche was created in this patient that rendered him vulnerable to one of the newly emerging molds, *Fusarium* species. The isolate was antifungal resistant except for susceptibility to voriconazole, to which he responded. This organism is ubiquitous in the environment, with Darwinian factors selecting for it to occupy a vacant ecologic niche. It is highly likely that increasing numbers of infections ascribed to new and emerging fungi will be seen in the next decade in patients exposed to broad spectrum antimicrobial therapy that includes both antifungal and antibacterial drugs [9]. When this is combined with the presence of foreign bodies that breach mucocutaneous barriers, and an immunosuppressed state, opportunistic infection requiring new forms of therapy are to be expected.

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