Introduction to the Immunocompromised Host Society Consensus Conference on Epidemiology, Prevention, Diagnosis, and Management of Infections in Solid-Organ Transplant Patients

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Infectious complications are still a significant cause of morbidity and death in solid-organ transplant patients, with significant infection being found in up to two-thirds of these individuals. The risk of infection in the organ transplant patient, particularly of opportunistic infection, is largely determined by 3 factors: the net state of immunosuppression, the epidemiologic exposures the patient encounters, and the consequences of the invasive procedures to which the patient is subjected. The most important principles of patient treatment are prevention, early diagnosis, and specific therapy. This issue is designed as a position paper by a group of experts on epidemiology, prevention, diagnosis, and management of infections in solid-organ transplant patients. We feel that our efforts may serve as an important first step in the development of guidelines in this area.

Infection remains an important problem in organ transplantation, because of the direct infectious disease consequences of microbial invasion and the indirect consequences of local and systemic cytokine, growth factor, and chemokine release in response to such microbial invasion [1–3]. Whereas the direct consequences of microbial invasion—such as pneumonia, wound infection, bacteremia, abscess, or urinary tract infection—are well known to all practitioners [4–8], the indirect consequences are less well known but may be the dominant effect of infection in the individual patient. Among the most important possible indirect effects of infection are the following: an immunosuppressing effect that can open the door to opportunistic infection [2, 9–11], a role in the pathogenesis of allograft injury [12–15], and a role in the development of certain malignancies [16, 17]. As one approaches the question of prevention and treatment of infection in the transplant recipient, it is important to define what manifestations of a particular infection are being addressed. In general, far more information is available on the direct manifestations of infection than on the indirect ones.

The potential sources of infection in the transplant patient are extremely broad and include endogenous flora; contaminated air, water, and food; and direct contact with individuals carrying potential pathogens [18]. The last sources are particularly important within the hospital environment, because hospital-based outbreaks due to person-to-person spread with such organisms as methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant enterococci, *Clostridium difficile,* antibiotic-resistant gram-negative bacilli, and azole-resistant yeast species have had a particular impact on these vulnerable hosts [19]. The risk of infection in the organ transplant patient, particularly of opportunistic infection, is largely determined by 3 factors: the net

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state of immunosuppression, the epidemiologic exposures the patient encounters, and the consequences of the invasive procedures to which the patient is subjected [2].

The net state of immunosuppression is a complex function determined by the interaction of a number of factors [2]: the dose, duration, and temporal sequence of administration of immunosuppressive drugs; the presence or absence of leukopenia; breaches to the integrity of the mucocutaneous barriers to infection, devitalized tissue, or undrained fluid collections; the presence or absence of such metabolic factors as protein-caloric malnutrition, uremia, and, perhaps, hyperglycemia; and the presence or absence of infection with $\geq$1 of the known immunomodulating viruses (cytomegalovirus, Epstein-Barr virus, hepatitis B or C virus, HIV, and, perhaps, human herpesviruses 6 and 7). Although the nature of the immunosuppressive therapy is clearly the driving force in determining the risk of infection [10], some observations about the other factors underline their potential importance. More than 90% of opportunistic infections occur in individuals with preceding immunomodulation induced by viral infections. Indeed, the remaining 10% of infections usually turn out to be caused by an excessive environmental exposure to the pathogen. In the case of metabolic factors, if patients are stratified on the basis of a serum albumin level <2.5 g/dL, there is a $\leq$10-fold increase in the incidence of life-threatening infections in those who are hypoalbuminemic [20, 21].

Epidemiologic exposures will be considered in detail later in this issue. For our purposes, it is important to emphasize that exposures in both the community and the hospital must be considered, with both remote and recent exposures being of potential importance [18, 22]. A useful analogy is to liken the transplant patient to a "sentinel chicken" placed in a given environment. Any excess traffic in microbes will be seen and felt in this and other immunosuppressed patient populations.

Technical aspects of the organ transplant patient's management are of great importance in determining the risk of infection. Problems in the management of the surgery (leading to devitalized tissue, anastomotic disruption, or fluid collections), vascular access, an endotracheal tube, and drainage catheters markedly predispose the patient to potentially lethal infection [3]. Antimicrobial agents can provide a window of opportunity for correcting these problems. If this opportunity is not taken, however, antibiotics by themselves will only select for antimicrobial resistance. In transplant patients with surgically related infection, optimal treatment would combine surgical correction of the anatomic abnormality that led to the infection in the first place and aggressive antimicrobial therapy appropriate for the flora that are present.

Among the most important principles of antimicrobial therapy in the transplant patient is the recognition that the nature of any immunosuppressive therapy that the patient is receiving must be taken into account [2]. Under circumstances of increased immunosuppression, antimicrobial therapy will usually need to be intensified and/or extended. This is particularly true when dealing with viral and fungal infection. Indeed, it can be said that the therapeutic prescription for the transplant patient has 2 components: an immunosuppressive component, to prevent and treat rejection, and an antimicrobial component, to make immunosuppression safe. This antimicrobial component consists of both drugs and epidemiologic protection, including HEPA-filtered environments for those patients who are most severely immunosuppressed.

There is a timetable or stereotypical pattern according to which different infections occur after organ transplantation [23]. That is, although an infectious disease syndrome such as pneumonia can occur at any point in the posttransplant course, the etiology of the pneumonia will be very different at very different time points. The posttransplant timetable can be divided into 3 time periods [2, 18, 23]. During the first month after transplantation, >95% of the infections are due to bacterial or candidal infection of the surgical wound, vascular access, endotracheal tube, or drainage catheters. These infections are comparable to those observed in nonimmunosuppressed patients undergoing similar surgery. During the period 1–6 months after transplantation, 2 classes of infection are observed: infections caused by immunomodulatory viruses and infections caused by opportunistic pathogens such as *Pneumocystis carinii, Listeria monocytogenes,* and *Aspergillus* species. In the late period, >6 months after transplantation, the patient population can be divided into 3 subgroups: more than two-thirds of transplant patients have had a good result from transplantation and are primarily at risk from community-acquired respiratory viruses. Ten percent to 15% of transplant patients suffer from chronic viral infection, such as infection with hepatitis B or C virus, which progresses inexorably to end-stage organ dysfunction and/or cancer unless effective antiviral therapy can be administered. Finally, 5%–10% are "chronic ne'er do wells" who have relatively poor allograft function and who have received excessive amounts of immunosuppression. These patients are the subgroup at greatest risk of opportunistic infection, particularly with such organisms as *Cryptococcus neoformans, P. carinii,* and *L. monocytogenes.*

The usefulness of this timetable is 3-fold [2]. First, it assists in the formulation of a differential diagnosis for the individual patient with an infectious disease syndrome. Second, it is useful in infection control, because the identification of an exception to the timetable usually connotes an excessive environmental hazard. Finally, it is the basis of cost-effective infection-control strategies. Thus, in the first month after transplantation, perioperative surgical wound prophylaxis is important. For the period 1–6 months after transplantation, low-dose trimethoprim-sulfamethoxazole prophylaxis and cytomegalovirus prevention

Table 1. Rating system for the strength of each recommendation for antimicrobial treatment.

Category	Definition
A	Strong evidence for efficacy and substantial clinical benefit support recommendation for use; should always be offered
B	Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use; should in general be offered
C	Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy may not outweigh adverse consequences such as toxicity, drug interactions, or cost of the chemoprophylaxis or alternative approaches; optional
D	Moderate evidence for lack of efficacy or for adverse outcomes supports a recommendation against use; should in general not be offered
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use; should never be offered

NOTE. Based on the 1997 Infectious Diseases Society of America rating system [24, 25].

are central to patient management. And finally, trimethoprim-sulfamethoxazole and fluconazole are useful prophylaxis in the "chronic ne'er do well" population.

There are 3 modes in which antimicrobial therapy can be prescribed [2]: therapeutic, in which antimicrobial therapy is prescribed to treat clinically overt infection; prophylactic, in which an entire population is prescribed antimicrobial therapy before an event to prevent an infection that is common enough and important enough to justify such a commitment; and preemptive, in which antimicrobial therapy is prescribed before clinical infection is present to a subgroup of patients who have been shown to be at especially high risk of clinical infection on the basis of a clinicoepidemiologic characteristic or laboratory marker.

Antimicrobial therapy in any of the 3 modes is complicated by 2 factors. If a therapeutic course is required in these immunosuppressed individuals, extended courses of therapy are usually required, particularly for opportunistic pathogens. Second, the possibility of drug interactions with the 2 mainstays of modern immunosuppression, cyclosporine and tacrolimus, is very real and significantly affects the choice of antimicrobial. There are 3 categories of antimicrobial interaction with cyclosporine and tacrolimus. First, the antimicrobial agent (e.g., rifampin, isoniazid, and nafcillin) up-regulates the metabolism of the immunosuppressive drugs, resulting in decreased blood levels and an increased possibility of allograft rejection. Second, the antimicrobial agent (e.g., the macrolides erythromycin, clarithromycin, and, to a lesser extent, azithromycin or the azoles ketoconazole, itraconazole, and, to a lesser extent, fluconazole) down-regulate the metabolism of the immunosuppressive drugs, which results in increased blood levels and an increased possibility of nephrotoxicity and overimmunosuppression. And finally, there may be synergistic nephrotoxicity, when therapeutic levels of the immunosuppressive agents are combined with therapeutic levels of aminoglycosides, amphotericin, and vancomycin and high therapeutic doses of trimethoprim-sulfamethoxazole and fluoroquinolones.

The net effect of these various considerations is to emphasize the prevention of infection, with prophylactic or preemptive strategies, in conjunction with technically impeccable surgery, environmental protection, and appropriate immunosuppressive therapy.

This issue summarizes the results of a Consensus Conference on Epidemiology, Prevention, Diagnosis and Management of Infections in Solid Organ Transplant Patients held in Davos, Switzerland, in June 1998, under the auspices of the Immunocompromised Host Society. All the articles were updated in summer 2000. The recommendations discussed throughout the articles are rated by the use of a revised version of the Infectious Diseases Society of America rating system (tables 1 and 2) [24,

Table 2. Rating system for the quality of evidence supporting the recommendation for antimicrobial treatment.

Category	Definition
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from >1 center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Based on the 1997 Infectious Diseases Society of America rating system [24, 25].

25]. In this system, a letter rating (A–E) signifies the strength of the recommendation; a Roman numeral (I–III) indicates the quality of evidence supporting the recommendation.

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