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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cedures 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 leuko-
penia; 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 ≥1 of the known
immunomodulating viruses (cytomegalovirus, Epstein-Barr vi-
rus, hepatitis B or C virus, HIV, and, perhaps, human herpes-
viruses 6 and 7). Although the nature of the immunosuppres-
sive 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 op-
portunistic 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 ≤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 manage-
ment are of great importance in determining the risk of in-
fec tion. Problems in the management of the surgery (leading
to devitalized tissue, anastomotic disruption, or fluid collect-
ions), vascular access, an endotracheal tube, and drainage cath-
ers markedly predispose the patient to potentially lethal in-
fec tion [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 surgi-
cally related infection, optimal treatment would combine sur-
gical 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 ther-
apy 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 in-
creased 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 pre-
vent 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 di-
vided 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 pa-
tients undergoing similar surgery. During the period 1–6
months after transplantation, 2 classes of infection are observed:
infected caused by immunomodulatory viruses and infections
caused by opportunistic pathogens such as Pneumocystis carinii,
Listeria monocytogenes, and Aspergillus species. In the late pe-
riod, >6 months after transplantation, the patient population
can be divided into 3 subgroups: more than two-thirds of trans-
plant patients have had a good result from transplantation and
are primarily at risk from community-acquired respiratory vi-
ruses. 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 dysfunc-
tion and/or cancer unless effective antiviral therapy can be ad-
ministered. 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, peri-
operative surgical wound prophylaxis is important. For the pe-
riod 1–6 months after transplantation, low-dose trimethoprim-
sulfamethoxazole prophylaxis and cytomegalovirus prevention
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 pre-
emptive, 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 clinicopathologic characteristic or labor-
atory marker.

Antimicrobial therapy in any of the 3 modes is complicated
by 2 factors. If a therapeutic course is required in these immu-
nosuppressed individuals, extended courses of therapy are
usually required, particularly for opportunistic pathogens. Sec-
ond, 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 cyclo-
sporine and tacrolimus. First, the antimicrobial agent (e.g., ri-
fampin, 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, clar-
thromycin, 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 therape-
utic levels of the immunosuppressive agents are combined
with therapeutic levels of aminoglycosides, amphotericin, and
vancomycin and high therapeutic doses of trimethoprim-sul-
famethoxazole 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 Immuno-
compromised 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,
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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References