Introduction to the Guidelines

The transformation of organ transplantation from an interesting experiment in human immunobiology to the most practical means of rehabilitating patients with a variety of forms of end organ dysfunction may be the outstanding clinical accomplishment of the biomedical revolution that has occurred over the last three decades. Indeed, the rate of one year graft survival at many centers for nonpulmonary allografts approaches and even exceeds 90%, with the comparable statistic for lung allografts being ~75%. Despite this success, 50–75% of transplant patients will have evidence of microbial invasion in the first year post-transplant, with the consequences of such invasion being quite diverse, encompassing the following: *direct* consequences, in which the microbial invasion results in a variety of clinical infectious disease syndromes such as mononucleosis, pneumonia, gastroenteritis, hepatitis, etc. and *indirect* consequences, in which cytokines, chemokines, and growth factors elaborated by the transplant recipient in response to microbial replication and invasion contribute to the net state of immunosuppression, the pathogenesis of acute and chronic allograft injury, and even, in some cases, the development of malignancy. Given this array of clinical effects of infection in the transplant patient, the prevention (rather than the treatment of established clinical disease) has become a primary goal of practitioners of transplant infectious disease, and it is with this goal in mind that these guidelines have been prepared (1). In this analysis, the evidence-based rating systems for both the strength of recommendations and assessment of the quality of the evidence established by the Infectious Disease Society of America (Tables 1 and 2) are employed (2). These guidelines should be regarded in two ways, as the present state of the art and as an outline of a research agenda for the coming decade.

As one approaches these guidelines certain general principles merit particular attention.

1 What is to be prevented by a particular intervention must be clearly defined; that is, are you concerned just with the prevention of clinical infectious disease syndromes, or are you also interested in the prevention of indirect consequences of infection. For example, a variety of regimens have been brought forth in an effort to prevent the direct manifestations of cytomegalovirus (CMV) infection, with significant success. What is perhaps even more interesting are three separate reports suggesting that antiviral prophylaxis may have value in decreasing the incidence of acute and chronic allograft injury (1,3–5).

2 The risk of infection in the solid organ transplant patient is largely determined by the interaction of three factors: *technical/anatomic mishaps* that involve the transplant procedure itself, and such perioperative aspects of care as the management of vascular access, drains, and the endotracheal tube; *environmental exposures* (Table 3); and the patient's *net state of immunosuppression* (Table 4). In the case of technical/anatomic mishaps, the best way to prevent infection is to correct the anatomic abnormality under coverage of appropriate antimicrobial therapy; antimicrobial therapy by itself will just extend the incubation period at the price of inducing resistance (1,6).

3 When one is considering therapy in the transplant patient, the concept of the *therapeutic prescription* is very useful. This has two major components, an immunosuppressive component to prevent and treat rejection; and an antimicrobial component to make it safe. Thus, the nature of the antimicrobial program being administered must be closely linked to the nature and intensity of the immunosuppressive program required. 'One size does not fit all' (1,6).

4 There are three modes in which antimicrobial agents can be administered to the transplant recipient: a *therapeutic* mode, in which antimicrobial agents are administered in the treatment of established clinical infection (not the primary focus of these guidelines); a *prophylactic* mode, in which antimicrobial agents are administered to an entire population before an event in order to prevent the occurrence of an infection important enough to justify this intervention: and a *preemptive* mode, in which antimicrobial agents are administered to a subpopulation noted to be at particular risk of clinically important infection on the basis of clinical, epidemiologic, or laboratory markers. These guidelines will focus both on preventive strategies (prophylactic and preemptive) and also on the diagnosis and management of established infection.

5 Infection in the post-transplant period has a very stereotyped temporal pattern, a *timetable*; that is, although such clinical syndromes as pneumonia can occur at any time point post-transplant, the etiology will be very different at different time points. Figure 1 delineates the timetable for organ transplants in the absence of antimicrobial intervention. When preventative antimicrobial therapy fails to protect, a common clinical effect is to extend the incubation period. For example, in the case of CMV infection, in the absence of prophylaxis CMV induced clinical disease is most common 1–3 months post-transplant; when

Table 1: Evidence-based rating system used to determine strength of recommendations

Category	Definition	Recommendation
A	Strong evidence for efficacy and substantial clinical benefit	Strongly recommended
B	Strong or moderate evidence for efficacy, but only limited clinical benefit	Generally recommended
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches	Optional Optional
D	Moderate evidence against efficacy or for adverse outcome	Generally not recommended
E	Strong evidence against efficacy or of adverse outcome	Never recommended

Source: Adapted from CDC. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1999; 48(RR-10): 1–66.

Table 2: Evidence-based rating system used to determine quality of evidence supporting recommendation

Category	Definition
I	Evidence from at least one well-executed randomized controlled trial
II	Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled Analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Source: Adapted from CDC. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1999; 48(RR-10): 1–66.

prophylaxis is used, but fails, it is common for the disease to occur 4–8 months post-transplant (depending on the nature of the prophylaxis and the immunosuppressive regimen) (6,7).

When considering the timetable of infection post-transplant, three time periods are recognized, each with differing forms of infection: (1,6,7)

1 *First month post-transplant.* In the first month there are three major causes of infection: (a) infection that was present in the recipient pretransplant, with its impact now increased as a result of surgery, anesthesia, and immunosuppressive therapy; (b) infection conveyed with a contaminated allograft; and (c) the same bacterial and candidal infections of the wound, lungs, drainage catheters, and vascular access devices

Table 3: Epidemiologic exposures of importance for the organ transplant recipient

A. In the community
1. *Mycobacterium tuberculosis*
2. Geographically restricted systemic mycoses
    Blastomycosis
    Coccidioidomycosis
    Histoplasmosis
3. *Strongyloides stercoralis*
4. Respiratory viruses
    Influenza
    Parainfluenza
    Respiratory syncytial virus
    Adenoviruses
5. Infections acquired by the ingestion of contaminated food/water
    Salmonella species
    Campylobacter jejuni
    Listeria monocytogenes
    Giardia lamblia
6. Environmental fungi (*Aspergillus* species and others)
7. Vector-borne (e.g. West Nile virus)
B. In the hospital
1. From the contaminated air
    Aspergillus species
    Pseudomonas aeruginosa and other Gram negative bacilli
2. From contaminated potable water
    Legionella pneumophila
    Other *Legionella* species
3. Unwashed hands of medical personnel
    Candida species (including azole resistant)
    Methicillin resistant *Staphylococcus aureus*
    Vancomycin resistant enterococci
    Highly resistant Gram negative bacilli
C. Global travel (selected examples only)
1. Gastrointestinal bacterial and viral pathogens
    Salmonella, *Shigella*, *Campylobacter*, *Vibrio*
    E. coli (multiple types)
    Viral gastroenteritis (e.g. on cruise ships)
2. Parasitic infections
    Malaria
    Strongyloidiasis and other intestinal parasitic diseases
    Leishmaniasis
3. Respiratory infections
    SARS coronavirus
4. Viral hepatitis
    Hepatitis A,E
    Hepatitis B for long-term travel or residence

seen in nonimmunosuppressed patients undergoing comparable surgery (although the impact tends to be greater in transplant patients). More than 95% of the infections occurring in the first month post-transplant fall into this last category, with the number one factor determining the incidence of such infections being the technical skill with which the surgery and perioperative care is accomplished.

2 *One to six months posttransplant.* In this time period there are two major classes of infection: (a) this is the time period when the immunomodulating viruses (cytomegalovirus, Epstein-Barr virus, human

herpesvirus-6, and the hepatitis viruses (B and C) exert their direct effects; and (b) the combination of sustained immunosuppression and immunomodulating viral infection creates a net state of immunosuppression great enough that such opportunistic infections as *Listeria monocytogenes*, *Aspergillus fumigatus*, and *Pneumocystis jiroveci* can occur without an especially intensive environmental exposure.

3 *More than six months posttransplant.* These individuals can be divided into three categories: (a) the 80% of patients with a good result from transplantation (maintenance immunosuppression, good allograft function) are at greatest risk from community acquired respiratory viruses (e.g. influenza, parainfluenza, and respiratory syncytial virus); (b) the 10% of patients with chronic hepatitis infection will develop progressive liver failure and/or hepatocellular carcinoma unless effective antiviral therapy can be deployed; and (c) the 10% of patients with a poor outcome from transplantation (excessive acute and chronic immunosuppression, poor allograft function, and, often, chronic viral infection), a group that some experts have termed the 'chronic n'er do wells', is at highest risk for opportunistic infection with such organisms as *Pneumocystis jiroveci*, *Listeria monocytogenes*, *Cryptococcus neoformans*, and *Nocardia asteroides*.

The timetable is useful in three ways: in the differential diagnosis of a patient with a possible infectious disease syndrome; as an infection control device, as exceptions to the timetable are usually due to an unusual environmental hazard, often within the hospital; and, most important in the context of these guidelines, this timetable is the ba-

Table 4: Factors contributing to the net state of immunosuppression in the organ transplant recipient

1. Dose, duration, and temporal sequence of immunosuppressive therapy
2. Neutropenia, lymphocytopenia
3. Metabolic abnormalities
     Protein-calorie malnutrition
     Uremia
     Hyperglycemia
4. Infection with immunomodulating viruses
     Cytomegalovirus
     Epstein-Barr virus
     Human herpesvirus–6
     Hepatitis B virus
     Hepatitis C virus
     Human immunodeficiency virus

sis for designing focused, cost effective preventative antimicrobial strategies (1,6,7).

References

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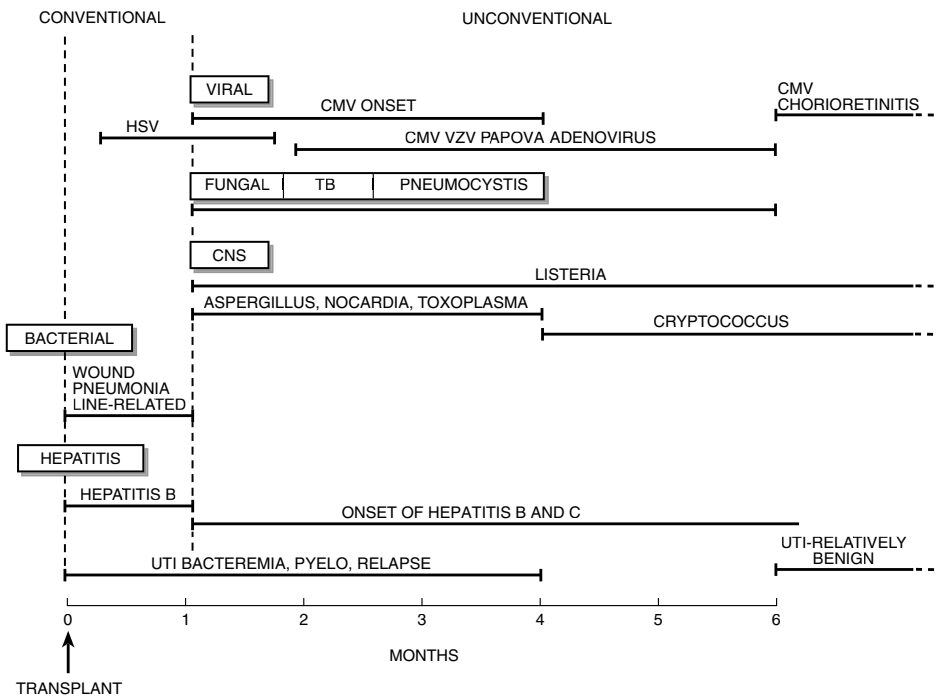
Figure 1: Timetable of infection following organ transplantation. Adapted from *Clinical Approach to Infection in the Compromised Host*, 4th edn. RH Rubin and LS Young (eds). Kluwer Academic/Plenum Publishers, New York, 2002.

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