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REVIEW

The prevention of infection post-transplant: the role of prophylaxis, preemptive and empiric therapy

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Summary

The close linkage of infection with the nature and intensity of the transplant immunosuppressive program has led to the concept of the therapeutic prescription. This has two components: an immunosuppressive one to prevent or treat rejection and graft-versus-host disease and an antimicrobial one to make it safe. This review provides a conceptual framework to approach the risk and risk periods for infection in solid organ and hematopoietic stem cell transplant recipients as well as an approach to antimicrobial use in this population.

Introduction

The stable restoration of function through allogeneic transplantation in patients with end-stage organ disease or malignancy remains a remarkable feat of medical care as we move into the 21st century. Although not universally available, such treatments have allowed many patients not only to avert death, but also to return to a life without obvious limitations. Such long-term success has been made possible by advances in a number of areas [1,2]:

1 Optimal tissue typing and matching and more individualized immunosuppressive regimens made possible by the definition of the unique challenges of each donor–recipient pair.

2 Careful donor evaluation and preparation, and proper preparation of the recipient (particularly, eradicating all treatable infection prior to transplant and controlling persistent infections post-transplant).

3 Impeccable technique in harvesting and transplanting the allograft (organ or hematopoietic stem cells), such that there is minimal tissue injury, secure anastomoses, prevention and aggressive drainage of fluid collections, as well as careful management of vascular access devices, endotracheal tubes, and drainage catheters.

4 Prevention of infection whenever possible with prophylactic or preemptive antimicrobial therapy, and prompt diagnosis and aggressive treatment of microbial invasion when prevention fails.

The net result has been improved control of rejection, graft-versus-host disease (GVHD) and infection (the major barriers to successful transplantation), and an expansion of clinical conditions that can be solved by transplantation. The close linkage of infection with the nature and intensity of the immunosuppressive program has led to the concept of the therapeutic prescription. This has two components: an immunosuppressive one to prevent or treat rejection and GVHD, and an antimicrobial one to make it safe. Implicit in this statement is the recognition that changes in the immunosuppressive strategy must trigger changes in the antimicrobial program [3].

The recognition of the enhanced susceptibility to infection in transplant recipients and its peculiar spectrum of agents and presentations have coevolved with these advances. The understanding of the molecular, clinical, epidemiological, and temporal basis of such risks and the development of strategies to prevent or minimize the deleterious consequences of infection has been an important factor in the overall advancement of transplantation. In the present review we provide a current conceptual framework for the prevention of infection or its consequences in the transplanted patient.

Risk of infection

Infection can be viewed as a probabilistic function of inoculum and virulence of a particular organism in an exposed susceptible host (Table 1). The range of organisms capable of causing infection in transplant recipients is quite broad. They lend themselves to a simple classification system: *true pathogens*, *sometime pathogens*, and nonpathogens (Table 1). *True pathogens* are the classic plagues of humankind (influenza, bubonic plague, smallpox, among others) which produce toxins, cross tissue planes and are able to evade the protection provided by innate immunity. Specific immunity or effective antimicrobial therapy is essential for their control. *Sometime pathogens* are those organisms that normally reside on mucocutaneous surfaces without clinical impact; injury to these surfaces provides access for these organisms to sites vulnerable to invasive infection (e.g., peritonitis after colonic perforation). *Nonpathogens* are those saprophytes that are ubiquitous in the environment and are kept in check by innate immune mechanisms, and only cause disease in the significantly immunocompromised (e.g., *Aspergillus* species, *Pneumocystis jiroveci*, and a variety of other microbial species). The term 'opportunistic infection' applies then to an invasive infection caused by a *nonpathogen* or to infection caused by an organism that causes a trivial infection in the normal host but life-threatening infection in the immunocompromised individual (e.g., *Candida* vaginitis versus disseminated candidiasis). Transplant patients are subject to all three classes of infection, with amplification of particular clinical syndromes by the immunosuppressed state [1].

Three factors should be considered when assessing the risk of infection in the transplant patient [1–5]:

1 Exposure, which can be environmental or endogenous. The inoculum size and organism virulence play an important role in the development of clinical infection after exposure. Environmental exposures can occur in the community or within the hospital. In the hospital, they can be domiciliary (exposure to contaminated air or water occurring in the room or ward where the patient is housed) or nondomiciliary (exposure occurring as the patient travels in the hospital) [6]. Person-to-person spread of such organisms as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and azole-resistant fungi on the hands of medical personnel is well documented and should be addressed by each transplant center. The best clue for the presence of an environmental hazard is the occurrence of significant infection at a time when the net state of immunosuppression should

Table 1. The considerations of infectious risks in transplant recipients.

Inoculum	Virulence	Net state of immunosuppression
Organ-derived	True pathogens	Immunosuppressive regimen
Herpesviruses (CMV, EBV)	*Variola major*	Steroids
Old granulomas (tuberculosis, histoplasmosis)	*Bacillus anthracis*	Calcineurin inhibitors
Subclinical (WNV, LCMV)	*Vibrio cholerae*	Sirolimus
Endogenous colonization	Sometime pathogens	Rejection and its treatment
Cystic fibrosis	*Staphylococcus aureus*	Antithymocyte globulin
Previous antimicrobial exposure	*Pseudomonas aeruginosa*	Alemtuzumab
Surgical and support techniques	*Candida* species	Balivizumab
Organ anastomosis and drains	Opportunists	Underlying diagnosis and its treatment
Vascular access	CMV	Hematologic malignancies
Environmental	*Toxoplasma gondii*	Rheumatologic diseases
Community versus hospital acquired	*Aspergillus fumigatus*	Immunomodulating viruses (CMV)
Domiciliary versus non-domiciliary		Age
		Nutrition
		Race, pharmacogenomics

Infection = inoculum × virulence × net-state-of-immunosuppression. Infection can be viewed as a probabilistic function of inoculum and virulence of a particular organism in an exposed susceptible host. See section on Risk of infection for further details.
CMV, cytomegalovirus; EBV, Ebstein-Barr virus; WNV, West Nile virus; LCMV, lymphocytic choriomeningitis virus.

not be great enough for this to occur without a particularly intense exposure [1,7]. Endogenous exposure is not only linked to previous colonization, but also to the presence of technical/anatomic factors related to the transplant procedure that lead to local vulnerability of invasive infection. Management of this problem requires correction of the abnormality in conjunction with appropriate antimicrobial therapy; antimicrobial agents alone will just select for resistance.

2 Darwinian competition that determines the nature of the infection that will invade these areas of vulnerability. The presence of particular organisms at a given site is the result of a selection process among different microbial species. Factors that provide a particular advantage to a given species include the following: the ability to adhere to specific receptors on epithelial surfaces; availability of nutrients (e.g., excess glucose in secretions bathing mucosal surfaces will promote growth of *Candida* species); the presence of specific growth factors (e.g., iron excess providing an advantage to *Zygomycetes*, *Listeria monocytogenes*, and other organisms); and the selective pressures of broad spectrum antimicrobial agents (resulting in resistant species now competing effectively at a given site) [1].

3 A complex function termed the net state of immunosuppression, which is determined by the factors delineated in Table 1. The dose, duration and temporal sequence in which immunosuppressive regimens are administered is a driving force, but the importance of other factors is illustrated by the following observations: 90% of opportunistic infections occur in patients with immunomodulating viral infection (particularly cytomegalovirus, CMV); the remaining 10% are usually a clue to unrecognized environmental exposure; the risk of life-threatening infection rises 10-fold in those patients with serum albumin levels <2.4 g/dl; African–Americans appear to require and to tolerate more immunosuppression than other racial groups [8,9].

Timetable of infection

For both solid organ (SOT) and hematopoietic stem cell (HSCT) transplantation, protocols for managing immunosuppression have become sufficiently standardized that the time course of different infections can be delineated; that is, infectious disease syndromes such as pneumonia can occur at any time in the post-transplant course, but the etiology changes at different points in time (Figs 1

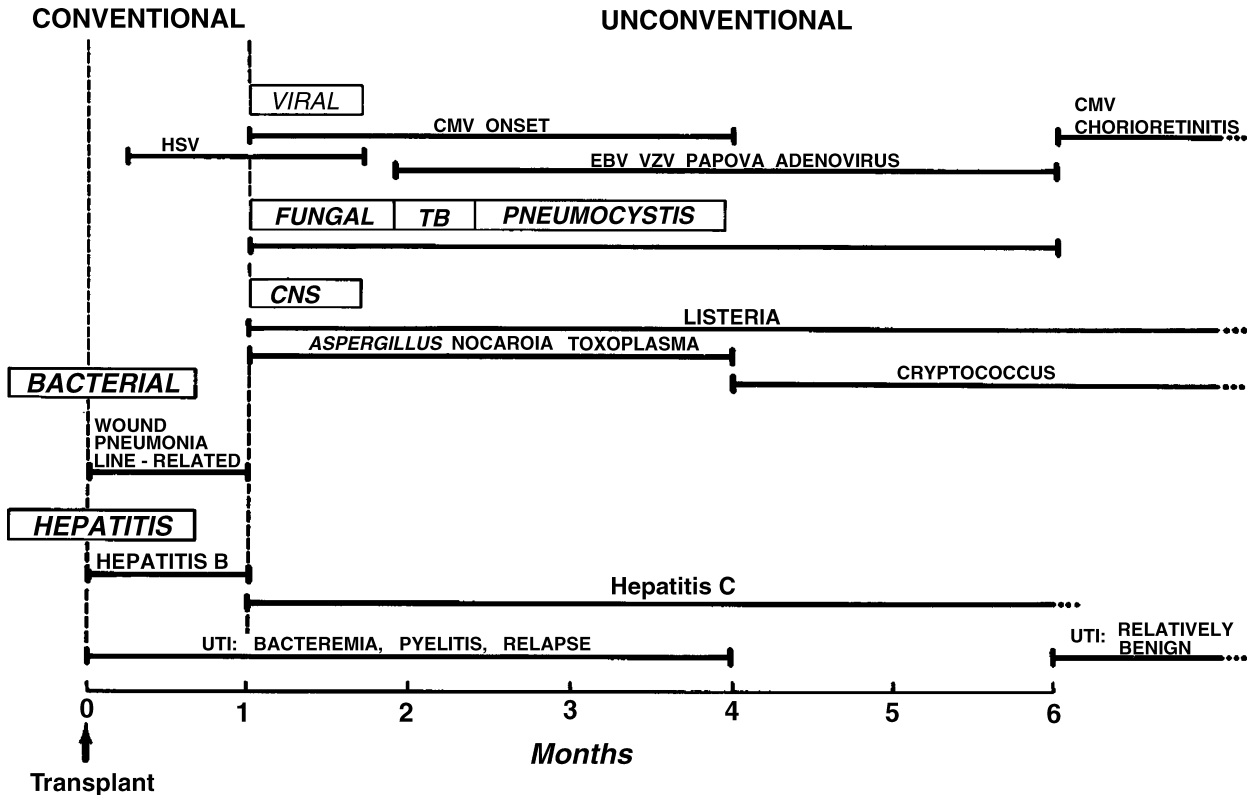

Figure 1 Timetable of infection after solid (renal) transplantation. HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; VZV, Varicella (Herpes) Zoster virus; Papova, papovaviruses (BK and JC); TB, tuberculosis.

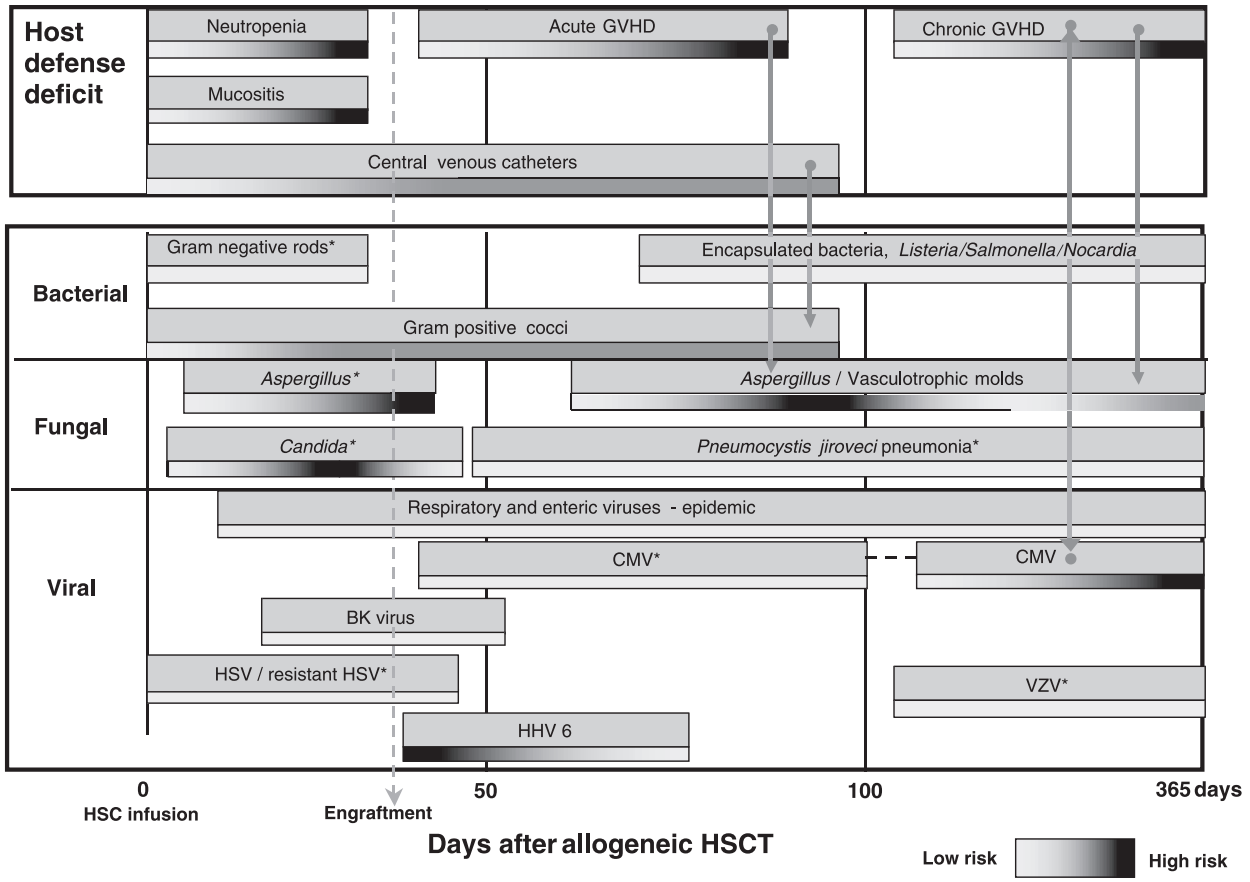

Figure 2 Timetable of infection after HSCT (adapted from Baden and Rubin [37]). Infections are graphed in relation to evolving underlying host defects during the transplantation process. The risk density in represented by the bar underlying a specific pathogen(s). *Highlights microorganisms for which a established antimicrobial strategy is commonly used in clinical practice. GVHD, graft-versus-host disease; HHV6, human herpesvirus-6.

and 2). This information is useful in several ways: in constructing the differential diagnosis for a patient who presents with an infectious disease syndrome; as a guide to infection control as exceptions to the timetable usually connote the presence of an unsuspected environmental hazard; and as the foundation for cost-effective preventive strategies [1–4].

In the SOT patient, it is useful to divide the timetable into three periods (Fig. 1) [10].

First month post-transplant

There are three categories of infection during this period: (i) unresolved infection present in the recipient prior to transplantation and exacerbated by the transplant operation or immunosuppression (particularly in patients that received immunosuppression prior to SOT for treatment of their underlying disease); (ii) donor-derived infections that are usually the result of terminal illnesses, critical care or that are acquired in the procurement, transport and implantation of the organ [11]. In addition, non-herpesvirus asymptomatic or undiagnosed infections such as human immunodeficiency virus (HIV), rabies, lymphocytic virus and West Nile virus have been transmitted from the donor to allograft recipients [11–15]; and (iii) infection caused by the same microorganisms that cause perioperative infection in nonimmunosuppressed patients undergoing comparable surgery. More than 95% of infections occurring in transplant patients are of this last type, with their incidence being determined by the technical skill in which surgery is accomplished, and how endotracheal tubes, vascular access devices, and drainage catheters are managed [1].

Notable by their absence in this time period are opportunistic infections. Although the initial doses of immunosuppressive drugs are high, the net state of immunosuppression is not great enough for these to occur unless there is a particularly intense environmental exposure to such opportunists as *Aspergillus* or other angioinvasive moulds, *Listeria*, or *Nocardia*. Thus, the net

state of immunosuppression is primarily determined by the sustained level of immunosuppression (the area under the curve), and not by the daily dose of a particular drug. Prevention of infection in this time period is accomplished by technically impeccable surgery (resulting in a minimum of devitalized tissue and undrained fluid collections) and postoperative management of vascular access, drainage catheters and endotracheal tubes; perioperative antibiotics aimed at preventing surgical site infection; and the initiation of trimethoprim–sulfamethoxazole prophylaxis [1,10].

One to six months post-transplant

There are three categories of infection present in this period: lingering infection acquired earlier, often in association with residual technical/anatomic abnormalities; the direct consequences of certain virus infection [CMV, Epstein–Barr virus (EBV), human herpesvirus-6, hepatitis B and C, and the HIV]; and opportunistic infection due to such organisms as *Pneumocystis jiroveci* and *Aspergillus fumigatus*. Such infections are made possible by sustained immunosuppression and the immunomodulating effects of the co-infecting viruses. Indeed, more than 90% of the opportunistic infections in SOT patients occur in individuals with infection with one or more of these viruses [10,16,17]; in contrast, the absence of viral infection in a patient with opportunistic infection suggests an excessive environmental source. Prevention of infection during this period requires noncontaminated air and potable water supply, trimethoprim–sulfamethoxazole prophylaxis (which significantly reduces urosepsis [18,19], *Pneumocystis* [20,21], *Listeria* [22], and *Toxoplasma* [23] infection); and control of CMV replication and invasion with either a prophylactic or preemptive strategy [24–26].

More than 6 months post-transplant

In this period, the causes of infection can be divided into three general categories: (i) the >80% of patients with a good result from transplantation (minimal immunosuppression, good allograft function, and freedom from viral infection) are most at risk from infection with community-acquired respiratory viruses (e.g., influenza, parainfluenza, and respiratory syncytial virus); (ii) the approximately 10% of patients with chronic hepatitis C and B; unless antiviral therapy is effective, these patients are subject to progressive liver disease and hepatocellular cancer. Over the last decade, we have observed great progress in the management of patients who undergo liver transplantation because of hepatitis B. Thanks to the use of hyperimmune hepatitis B immunoglobulin and the use of antivirals active against hepatitis B (lamivudine, adefovir), these patients now experience a survival comparable with non-infected patients [27]. The management of hepatitis C remains a challenge [28]. (iii) Approximately 10% of patients who have had a relatively poor outcome from their transplant (repeated episodes of acute and chronic allograft injury; excessive immunosuppression; and chronic viral infection). These individuals, whom we have termed the *chronic n'er do wells*, are at the highest risk for opportunistic infection [1].

Preventive strategies used in all long-term transplant patients include influenza immunization and avoidance of environmental hazards. These hazards include gardening, community cleaning activities, exposure to construction, adventure travel to the developing world and contact with individuals with active transmissible infections. In the special situation of the *chronic n'er do wells*, lifelong trimethoprim–sulfamethoxazole and a consideration of fluconazole prophylaxis is appropriate [1,10].

There are two unique determinants of the infectious disease complications of HSCT [2]: the rate at which bone marrow and immune reconstitution occur, and whether or not significant GVHD is occurring. The duration of the granulocytopenia (the effects of which are amplified by the impaired barrier function of the gastrointestinal mucosa caused by the conditioning regimen) is in part related to the nature of the transplant: 20–30 days with the infusion of bone marrow, 10–20 days for peripheral blood stem cells, and 15–30 days with umbilical cord blood transplant [2]. The use of nonmyeloablative conditioning regimens that allow HSCT in patients who would not be otherwise eligible for HSCT, minimizes the period and intensity of neutropenia and mucositis (usually <1 week), but the overall risk of infectious complications, especially due to opportunists is not decreased [29–31]. Various maneuvers to deplete T cells *in vitro* before infusion, will delay further the recovery of lymphocytes, monocytes, and dendritic cells, and increase the risk of clinical CMV and EBV infection [32,33]. GVHD and its treatment results in a severe deficit in cell mediated immunity, and increased difficulty with herpes group viruses (particularly CMV) and fungi [29,31,34]. The same environmental exposures and vascular access issues that are important in SOT patients are important in HSCT recipients as well [35].

The timetable of infection for HSCT patients, then, can be divided into three distinct phases (Fig. 2) [36,37].

Phase 1

Phase 1 is the period of profound granulocytopenia and mucositis, beginning with the conditioning regimen and continuing until engraftment occurs. The infectious disease consequences can be considered in two general

categories: residual infection from the pretransplant experience, with invasive aspergillosis being the best example of this [38]; and infection, particularly of the bloodstream, related to breaks in the integrity of mucocutaneous surfaces. The organisms include gram positives (streptococci and staphylococci) and gram negatives (the Enterobacteriaceae and *Pseudomonas aeruginosa)*, as well as *Candida* species. As the period of granulocytopenia continues, the incidence of angioinvasive mold infection (e.g., invasive aspergillosis, *Scedosporium, Fusarium*, and others) rises significantly, emphasizing the key role of granulocytes in defending against infection with these organisms. Proposed preventive strategies include systematic use of protective gear (mask and gloves) by healthcare providers, HEPA filtration and positive pressure ventilation of patient rooms, and administration of prophylactic fluoroquinolones and systemic antifungals, depending on the rates of infection from particular conditioning regimens at a particular hospital [2,37]. A novel approach that warrants further exploration, is the use of palifermin, a recombinant keratinocyte growth factor. In a recently published randomized trial, palifermin administration at the time of conditioning chemotherapy significantly reduced the degree and severity of mucositis; the incidence of bloodstream infections was 15% in the palifermin group and 25% in placebo recipients [39].

Phase 2

Phase 2 is the period between engraftment and day 100. This is the peak time period for reactivation of the herpes group viruses, especially CMV. If engraftment is delayed, then the incidence of invasive fungal infections increases significantly. If specific anti-CMV preventive strategies are employed, then there can be a major delay (onset of CMV a year or more post-transplant) in the occurrence of this infection because of the partial protection provided by the preventive regimen [2,37].

Phase 3

This period (more than 100 days post-transplant) is dominated by whether or not GVHD is occurring, with its requirement for more intense and prolonged immunosuppression. In the absence of GVHD, the major problems include varicella-zoster virus and pneumococcal and respiratory virus infection, because of immaturity in immune function. In addition, late onset CMV, either because of relapsing infection or, more commonly, because of partially effective preventive therapy which greatly extended the incubation period. A profound deficit in microbial specific cell-mediated immunity as a consequence of GVHD and its treatment, results in a significant risk of infection with CMV, *Pneumocystis jirovecii*, and invasive fungi, as well as other organisms.

The increased incidence of invasive aspergillosis in patients with GVHD requiring immunosuppression emphasizes that there are two host defenses of importance against the invasive molds: functioning granulocytes in adequate numbers and intact cell-mediated immunity. Thus, there are two peaks of incidence of invasive mold infection: pre-engraftment (in the presence of severe and persistent granulocytopenia) and postengraftment (in those patients with severe GVHD) [31,34].

Principles of antimicrobial use in transplant recipients

It is fair to say that without the intelligent deployment of antimicrobial agents both preventively and therapeutically modern transplantation would be impossible. There are a number of general principles that underlie the effective use of antimicrobial agents [40].

1 There are four different modes in which antimicrobials can be prescribed in order to prevent and treat infection:

(**A**) *Therapeutic*: the treatment of established clinical infection, with the ideal result being eradication of infection and prevention of relapse. Strict guidelines for duration of therapy are not available in the transplant population. Our approach is to treat until all evidence of infection (clinical, microbiological, and radiological) is eliminated, and then add a buffer period for safety. The length of this buffer period – not necessarily a prolonged one – depends on the importance of the infection, the potential consequences of relapse, the net state of immunosuppression, and the likelihood of favouring the emergence of resistant pathogens.

(**B**) *Prophylactic*: the administration of an antimicrobial program to an entire population of patients to prevent the occurrence of infection. For a prophylactic program to be useful, the infection(s) to be prevented have to be important, relatively frequent, and the prophylactic regimen must be inexpensive and well tolerated. By far the most effective prophylactic program for transplant patients is low dose trimethoprim–sulfamethoxazole, which has virtually eliminated *Pneumocystis*, toxoplasmosis, listeriosis, nocardiosis, and urosepsis from transplant recipients [18,21,23,41,42].

(**C**) *Empiric*: a form of treatment in which a fixed antimicrobial program is initiated on the basis of fever, unexplained hypotension or other signs of possible sepsis. In years past the preferred initial therapy was a combination of an appropriate beta-lactam and aminoglycoside (the choice as to which drugs are used being made on the basis of the known flora at a given hospital). With the

availability of drugs such as imipenem, ceftazidime, and piperacillin–tazobactam, single drug coverage for gram negatives has become common, particularly in stable patients [43]. Empiric therapy was developed to prevent the rapid deterioration that can be seen in this situation, particularly with gram-negative infection in the setting of neutropenia [44]. There is some controversy as to what drugs should be used empirically; the traditional approach is to treat for gram-negative infection and, if the patient is continuing to have signs and symptoms, to add additional gram-positive and antifungal empiric treatment [44,45], coupled with a systematic search for the source of the febrile syndrome. The use of empirical antifungal therapy during myeloablative HSCT has evolved over the last decade from therapies aimed mainly at *Candida* species that translocate from the gastrointestinal track after conditioning chemotherapy [45] to therapies that target both *Candida* and *Aspergillus* [46,47]. Empiric treatment regimens are used for a multitude of other scenarios and depend on the clinical syndrome (pneumonia, pyelonephritis, catheter-related bacteremia, meningitis), the time after transplantation when the syndrome occurs, and on information on the local and regional epidemiological experience where the patient is cared for (prevalence of methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *S. pneumoniae*, arthropod exposures, etc.).

(**D**) *Preemptive*: this form of therapy is based on the initiation of antimicrobial therapy to a fraction of the population at risk, who are asymptomatic, on the basis of a clinical epidemiologic characteristic or laboratory marker that connotes an increased risk of serious infection [26,48]. For example, studies of CMV infection in SOT patients have shown that CMV seropositive individuals treated with cyclosporine, azathioprine and prednisone have an incidence of symptomatic infection of approximately 10%; if they require OKT3 or antithymocyte globulin to treat rejection, then the incidence of CMV disease increases to approximately 50% or more [49]; if ganciclovir is prescribed with the initiation of the antilymphocyte antibody therapy, and continued for 3 months, then symptomatic disease is eliminated completely: it is preempted. Replicating CMV can be detected by blood antigenemia or polymerase chain reaction assays several days before symptomatic disease occurs, allowing one to intervene and preempt the occurrence of symptomatic disease on the basis of a biomarker. Similarly, respiratory tract colonization with *Aspergillus* species increases the risk of subsequent invasive disease significantly, and should be preempted if found early after transplantation or in those with significant GVHD [50]. As a general rule, developing biomarkers that predict subsequent clinical illness are needed for preemptive specific treatment of infections so that the need for unnecessary broad-spectrum (and at times ineffective) empiric therapy can be reduced.

2 Antimicrobial therapy should be deployed in different phases, even in the same patient, based on certain clinical scenarios. The first factor to be considered is to assess whether or not the patient has a therapeutic emergency or a diagnostic dilemma. If the former, then immediate assessment and culturing should be accomplished and broad-spectrum antimicrobials are initiated. Instead of serial deployment of antimicrobial agents, all reasonable therapies are initiated immediately, with a particular emphasis on bactericidal therapies if the patient is granulocytopenic. Issues of cost and toxicity are of secondary importance at this point in time; the only concern is the resuscitation of this critically ill individual. By day 3–5 the resuscitation should be nearly complete, and potentially useful information should be available from the laboratory, so reassessment of the antimicrobial program is in order: decrease in the number of drugs and their toxicity and targeted treatment for a specific pathogen; finally, one to two weeks later decisions regarding maintenance or suppressive therapy can be made. To describe these periods of time, we have borrowed from the oncology nomenclature: induction therapy for the therapeutic emergency and to gain control of specific infections; consolidation therapy after the patient has been stable or rehabilitated; and, finally, maintenance therapy to suppress infection or as secondary prophylaxis if necessary. Other than the absolute requirement for bactericidal therapy if the patient is granulocytopenic, a variety of drugs can be used. The cardinal rule here is that 'there are no points for neatness.' The choice of antibiotics should be made and reviewed at each of the three phases of therapy.

3 A landmark event in the history of transplantation was the development and deployment of the calcineurin inhibitors, cyclosporine and tacrolimus, in the 1980s. The one-year survival of cadaveric kidney transplants jumped from 50% to >85% in most centers. Not that these drugs are panaceas: renal toxicity, hypertension, and other toxicities are common. Perhaps the biggest problem is the occurrence of drug interactions, particularly with antimicrobial agents. The clinician caring for transplant recipients must develop a systematic way of addressing these drug interactions when prescribing antimicrobials and other treatments. There are three classes of drug interactions that are seen (at least two of which are because of effects on hepatic cytochrome 450 metabolism of the calcineurin inhibitors). All these interactions occur in the face of desired therapeutic blood levels of these drugs.

(**A**) Some antimicrobial agents (most notably rifampin, isoniazid, and nafcillin) induce the metabolism of the calcineurin inhibitors, resulting in inadequate blood levels

and an increased risk of rejection or exacerbations of GVHD.

(**B**) Some antimicrobial agents (most notably the macrolides and the antifungal azoles) inhibit the metabolism of the calcineurin inhibitors, resulting in high blood levels, renal injury, excessive immunosuppression, and an increased risk of opportunistic infection. Both of these interactions can be managed by dose adjustment and frequent measurement of cyclosporine and tacrolimus blood levels, particularly at the beginning and after the completion of antibiotic therapy.

(**C**) Synergistic renal toxicity. As the mechanisms by which these toxicities occur are not well understood, we describe them on the basis of their clinical presentation: (i) dose-related renal toxicity: whereas drugs such as trimethoprim–sulfamethoxazole are well tolerated at lower doses, at higher doses renal toxicity may occur; (ii) idiopathic toxicity with the occurrence of oliguric renal failure with a single dose of gentamicin or amphotericin in the face of therapeutic blood levels of the calcineurin inhibitors; and (iii) synergistic nephrotoxicity with gentamicin, vancomycin, and amphotericin: that is, nephrotoxicity occurring days to weeks before it would occur in the absence of cyclosporine and tacrolimus.

Conclusion

The therapeutic prescription for the transplant patient has two components: an immunosuppressive program to prevent and treat rejection and GVHD, and an antimicrobial program to make it safe. Changes in one of these necessitate changes in the other. The emphasis in transplant patients should be on the prevention of infection and, if this fails, surveillance and preemption of subclinical infection or early recognition and aggressive therapy of clinical infection. For virtually all infections in these patients, prognosis is related to how early in the disease process diagnosis is made.

As one looks into the future, it is likely that antimicrobial therapy will be closely linked to biomarkers that specify the risk for particular infections, microbial load and the presence of antimicrobial resistance. The term 'disease management program' will apply to the management of infection.

References

1. Rubin RH. Infection in the organ transplant recipient. In: Rubin RH, Young LS, eds. *Clinical Approach to Infection in the Compromised Host*. New York: Kluwer Academic/Plenum, 2002: 573–679.
2. Boeckh M, Marr KA. Infection in hematopoietic stem cell transplantation. In: Rubin RH, Young LS, eds. *Clinical Approach to Infection in the Compromised Host*. New York: Kluwer Academic/Plenum, 2002: 527–571.
3. Rubin RH, Ikonen T, Gummert JF, Morris RE. The therapeutic prescription for the organ transplant recipient: the linkage of immunosuppression and antimicrobial strategies. *Transpl Infect Dis* 1999; **1**: 29.
4. Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. *Am J Med* 1981; **70**: 405.
5. Rubin RH. Infectious disease complications of renal transplantation. *Kidney Int* 1993; **44**: 221.
6. Hopkins CC, Weber DJ, Rubin RH. Invasive aspergillus infection: possible non-ward common source within the hospital environment. *J Hosp Infect* 1989; **13**: 19.
7. Rubin RH. The compromised host as sentinel chicken. *N Engl J Med* 1987; **317**: 1151.
8. Meier-Kriesche HU, Friedman G, Jacobs M, *et al.* Infectious complications in geriatric renal transplant patients: comparison of two immunosuppressive protocols. *Transplantation* 1999; **68**: 1496.
9. Meier-Kriesche HU, Ojo A, Magee JC, *et al.* African-American renal transplant recipients experience decreased risk of death due to infection: possible implications for immunosuppressive strategies. *Transplantation* 2000; **70**: 375.
10. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; **338**: 1741.
11. Gottesdiener KM. Transplanted infections: donor-to-host transmission with the allograft. *Ann Intern Med* 1989; **110**: 1001.
12. Iwamoto M, Jernigan DB, Guasch A, *et al.* Transmission of West Nile virus from an organ donor to four transplant recipients. *N Engl J Med* 2003; **348**: 2196.
13. Kumar D, Tellier R, Draker R, Levy G, Humar A. Severe Acute Respiratory Syndrome (SARS) in a liver transplant recipient and guidelines for donor SARS screening. *Am J Transplant* 2003; **3**: 977.
14. Centers for Disease Control and Prevention. Lymphocytic choriomeningitis virus infection in organ transplant recipients, Massachusetts, Rhode Island. *MMWR Morb Mortal Wkly Rep* 2005; **54**: 537.
15. Srinivasan A, Burton EC, Kuehnert MJ, *et al.* Transmission of rabies virus from an organ donor to four transplant recipients. *N Engl J Med* 2005; **352**: 1103.
16. Singh N. Interactions between viruses in transplant recipients. *Clin Infect Dis* 2005; **40**: 430.
17. Singh N, Wannstedt C, Keyes L, *et al.* Indirect outcomes associated with cytomegalovirus (opportunistic infections, hepatitis C virus sequelae, and mortality) in liver-transplant recipients with the use of preemptive therapy for 13 years. *Transplantation* 2005; **79**: 1428.
18. Tolkoff-Rubin NE, Cosimi AB, Russell PS, Rubin RH. A controlled study of trimethoprim-sulfamethoxazole prophylaxis of urinary tract infection in renal transplant recipients. *Rev Infect Dis* 1982; **4**: 614.

19. Tolkoff-Rubin NE, Rubin RH. Urinary tract infection in the immunocompromised host. Lessons from kidney transplantation and the AIDS epidemic. *Infect Dis Clin North Am* 1997; **11**: 707.
20. Fox BC, Sollinger HW, Belzer FO, Maki DG. A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: clinical efficacy, absorption of trimethoprim-sulfamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. *Am J Med* 1990; **89**: 255.
21. Torre-Cisneros J, De la Mata M, Pozo JC, *et al.* Randomized trial of weekly sulfadoxine/pyrimethamine versus daily low-dose trimethoprim-sulfamethoxazole for the prophylaxis of *Pneumocystis carinii* pneumonia after liver transplantation. *Clin Infect Dis* 1999; **29**: 771.
22. Tolkoff-Rubin NE, Rubin RH. Opportunistic fungal and bacterial infection in the renal transplant recipient. *J Am Soc Nephrol* 1992; **2**: S264.
23. Baden LR, Katz JT, Franck L, *et al.* Successful toxoplasmosis prophylaxis after orthotopic cardiac transplantation with trimethoprim-sulfamethoxazole. *Transplantation* 2003; **75**: 339.
24. Egan JJ, Lomax J, Barber L, *et al.* Preemptive treatment for the prevention of cytomegalovirus disease: in lung and heart transplant recipients. *Transplantation* 1998; **65**: 747.
25. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. *Clin Infect Dis* 2001; **32**: 742.
26. Singh N, Wannstedt C, Keyes L, *et al.* Efficacy of valganciclovir administered as preemptive therapy for cytomegalovirus disease in liver transplant recipients: impact on viral load and late-onset cytomegalovirus disease. *Transplantation* 2005; **79**: 85.
27. Roche B, Samuel D. Treatment of hepatitis B and C after liver transplantation. Part 1, hepatitis B. *Transpl Int* 2005; **17**: 746.
28. Roche B, Samuel D. Treatment of hepatitis B and C after liver transplantation. Part 2, hepatitis C. *Transpl Int* 2005; **17**: 759.
29. Junghanss C, Marr KA, Carter RA, *et al.* Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. *Biol Blood Marrow Transplant* 2002; **8**: 512.
30. Fukuda T, Boeckh M, Carter RA, *et al.* Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003; **102**: 827.
31. Marty FM, Lee SJ, Fahey MM, *et al.* Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. *Blood* 2003; **102**: 2768.
32. Boeckh M, Nichols WG, Papanicolaou G, *et al.* Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. *Biol Blood Marrow Transplant* 2003; **9**: 543.
33. Hebart H, Einsele H. Clinical aspects of CMV infection after stem cell transplantation. *Hum Immunol* 2004; **65**: 432.
34. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood* 2002; **100**: 4358.
35. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep* 2000; **49**: 1.
36. Meyers JD. Infection in bone marrow transplant recipients. *Am J Med* 1986; **81**: 27.
37. Baden LR, Rubin RH. Infection in the hematopoietic stem cell transplant recipient. In: Soiffer RJ, ed. *Stem Cell Transplantation for Hematologic Malignancies*. Totowa, NJ: Humana Press, 2004: 237–258.
38. Fukuda T, Boeckh M, Guthrie KA, *et al.* Invasive aspergillosis before allogeneic hematopoietic stem cell transplantation: 10-year experience at a single transplant center. *Biol Blood Marrow Transplant* 2004; **10**: 494.
39. Spielberger R, Stiff P, Bensinger W, *et al.* Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004; **351**: 2590.
40. Baden LR, Teplick R, Rubin RH. Antimicrobial therapy. In: Parrillo JE, Dellinger RP, eds. *Critical Care Medicine: Principles of Diagnosis and Management in the Adult*. St Louis, MO: Mosby, 2001: 1047–1068.
41. Colby C, McAfee S, Sackstein R, *et al.* A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as Pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; **24**: 897.
42. Janner D, Bork J, Baum M, Chinnock R. *Pneumocystis carinii* pneumonia in infants after heart transplantation. *J Heart Lung Transplant* 1996; **15**: 758.
43. Pizzo PA, Hathorn JW, Hiemenz J, *et al.* A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; **315**: 552.
44. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982; **72**: 101.
45. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med* 1989; **86**: 668.
46. Walsh TJ, Teppler H, Donowitz GR, *et al.* Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; **351**: 1391.

47. Walsh TJ, Finberg RW, Arndt C, *et al.* Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999; **340**: 764.
48. Hibberd PL, Tolkoff-Rubin NE, Conti D, *et al.* Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. *Ann Intern Med* 1995; **123**: 18.
49. Hibberd PL, Tolkoff-Rubin NE, Cosimi AB, *et al.* Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. *Transplantation* 1992; **53**: 68.
50. Perfect JR, Cox GM, Lee JY, *et al.* The impact of culture isolation of Aspergillus species: a hospital-based survey of aspergillosis. *Clin Infect Dis* 2001; **33**: 1824.