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MINIREVIEW

Antimicrobial Strategies in the Care of Organ Transplant Recipients

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The dominant principle in the practice of transplantation infectious disease is that infection and rejection are inextricably intertwined, linked by the immunosuppressive therapy required to maintain allograft function. Any intervention that decreases the risk of infection, thus permitting more intensive immunosuppressive therapy, will increase the rate of allograft survival without threatening the patient's survival; conversely, any intervention that decreases the need for immunosuppressive therapy will lower the risk and consequences of infection without threatening the survival of the allograft. Thus, the therapeutic prescription for a transplant patient has two components: the immunosuppressive program and an antimicrobial strategy to render the immunosuppressive therapy safe (45).

There are three different modes in which antimicrobial drugs can be used: a *therapeutic mode*, in which antimicrobial agents are administered to treat established disease; a *prophylactic mode*, in which nontoxic antimicrobial agents are administered to all individuals to prevent an infection that is both common enough and important enough to merit such an approach; and a *preemptive mode*, in which antimicrobial agents are administered to a subgroup of patients prior to the appearance of clinical disease. The last mode is predicated on the use of a laboratory marker or patient characteristic that identifies that subgroup of individuals with the highest risk of serious disease at a time when antimicrobial intervention would be maximally effective in aborting the disease process (44).

Because the consequences of infection can be so devastating in transplant patients, the emphasis of this minireview (as it is in clinical practice) is on the prophylactic and preemptive strategies that can be used to prevent clinical infection.

ANTIMICROBIAL STRATEGIES AGAINST VIRAL INFECTION IN THE ORGAN TRANSPLANT RECIPIENT

The most important single infection in transplant recipients is that caused by cytomegalovirus (CMV), which not only is directly responsible for a variety of infectious disease syndromes (fever, pneumonia, hepatitis, gastrointestinal ulcerations, etc.) but also contributes significantly to the patient's net state of immunosuppression and may be involved in the pathogenesis of allograft injury (43). Three major patterns of CMV transmission, each with a different risk of clinical disease, are observed, as follows: primary infection, in which a CMV-seronegative individual receives cells latently infected with the virus from a seropositive donor and then reactivates the virus posttransplantation; reactivation infection, in which endogenous latent virus is reactivated in a CMV-seropositive individual posttransplantation; and superinfection, in which a seropositive recipient receives latently infected cells from a seropositive donor and the virus that reactivates posttransplantation is of donor origin. More than 90% of the time the exogenous, latently infected cells are present in the allograft itself; however, particularly in situations such as liver transplantation, in which prodigious amounts of blood products may be administered, viable leukocyte-containing transfusions derived from CMV-seropositive donors can transmit the virus. Approximately 60% of those at risk for primary infection, 20% of those at risk for reactivation infection, and an estimated 20 to 40% of those at risk for CMV superinfection become clinically ill—with more than 90% of these illnesses occurring 3 weeks to 4 months posttransplantation (26, 43, 49).

Given the protean manifestations of CMV infection in the transplant patient, great attention has been devoted to the treatment and prevention of this infection. Ganciclovir by itself has been shown to have significant benefit in the treatment of clinical CMV disease, particularly in patients without CMV pneumonia, severe gastrointestinal disease, or prolonged leukopenia (8, 12, 13, 26, 31, 42, 43). Studies in a murine model of CMV (46) and bone marrow transplant recipients with CMV pneumonia (14, 40) have shown that the combination of CMV hyperimmune globulin and ganciclovir is far more effective in treating disease than is either agent by itself. Although there is incomplete information for organ transplant recipients comparing ganciclovir alone with the combination (13, 43, 45), it is our policy to use combination therapy in organ transplant patients with the more severe manifestations of CMV disease. Although foscarnet (trisodium phosphonoformate) has been shown to have efficacy in the treatment of AIDS and bone marrow transplant patients with CMV infection, particularly infections with ganciclovir-resistant strains, the toxic-therapeutic ratio for this drug in organ transplant patients remains to be defined. Fortunately, ganciclovir resistance of CMV isolates has not yet been an important problem in organ transplant recipients (1, 10, 26, 29, 37, 41, 54).

A variety of prophylactic programs that use high-dose acyclovir administered orally (2, 4, 17, 63), both CMV hyperimmune (33, 49, 50) and standard immunoglobulin (51, 52), and the combination of these two approaches (36, 53), as well as ganciclovir (3, 32), have been studied for the prevention of the different patterns of CMV transmission in patients undergoing the various types of organ transplantation (Table 1). Although the data base is quite incomplete because of

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TABLE 1. Estimated efficacies of different prophylactic antiviral strategies against CMV infection in different forms of organ transplantation[a]

Type of transplant	Form of CMV infection	Antimicrobial strategy used	Estimated efficacy	Reference
Kidney	Primary	CMV hyperimmune globulin	2+	50
		High-dose acyclovir	2+	3, 4, 17
		CMV hyperimmune globulin + moderate-dose acyclovir	3+	36
	Secondary[b]	High-dose acyclovir	3+	3, 4, 17
		CMV hyperimmune globulin + moderate-dose acyclovir	3+	36
Heart and/or lung	Primary	High-dose ganciclovir (1 mo)	0	2, 32
	Secondary[b]	High-dose ganciclovir (1 mo)	4+	2, 32
Liver	Primary	CMV hyperimmune globulin	0	49
	Secondary[b]	CMV hyperimmune globulin	3+	49

[a] Unless otherwise noted, the regimens outlined were administered for a minimum of 3 months. Only semiquantitative assessments of efficacy are given, because of the recognition that the type of immunosuppression used will have a major effect on the efficacy of each of these regimens.

[b] Patients were not differentiated in the studies as to whether they had reactivation or superinfection; all patients seropositive for CMV prior to transplantation are grouped together.

different immunosuppressive regimens as well as different antiviral doses, we believe that the following tentative conclusions are warranted at the present time.

(i) High-dose acyclovir administered orally, as well as hyperimmune globulin (and perhaps standard immunoglobulin), administered singly or in combination over a period of 4 months has considerable efficacy in decreasing the incidence of primary CMV disease in renal transplant patients being immunosuppressed with cyclosporine, prednisone, and azathioprine. However, there is significantly less efficacy when antilymphocyte antibody therapies (e.g., antithymocyte globulin, antilymphocyte serum, or OKT3) are added to the immunosuppressive programs for these patients. Unfortunately, there is little evidence that any of these prophylactic programs, or even ganciclovir administered for 1 month posttransplantation, has any effect on the occurrence of primary CMV disease following heart, lung, or liver transplantation (2–4, 17, 32, 33, 36, 49–53).

(ii) Prevention of CMV disease in seropositive allograft recipients (at risk for either reactivation or superinfection disease) appears to be possible with any of these regimens, particularly when antilymphocyte antibody therapies are not used (2, 4, 17, 32, 33, 36, 49–53).

(iii) Definition of the optimal doses and the duration of each of these prophylactic programs has not yet been accomplished. In the case of acyclovir, prophylactic efficacy occurs when peak levels in blood are approximately 25 μmol/liter, in the face of an average 50% inhibitory concentration of approximately 45 μmol/liter (2, 4, 17), suggesting that inhibition of the virus is most easily accomplished as it emerges from latency and when only small amounts of replicating virus are present. In the case of intravenous immunoglobulin therapy, the nature of the protecting antibody, its epitopic specificity, and the titers necessary to protect the individual are currently unknown. Thus, it is not surprising that the relative merits of standard intravenous globulin and a preparation hyperimmune for anti-CMV antibodies, or their optimal doses, are currently unknown. Despite these unknowns, it is remarkable that even partial protection has been achieved with these prophylactic regimens. These issues will become even more important as monoclonal anti-CMV antibodies are developed. Studies in the murine model (15), as well as those defining the nature of circulating antibody in seropositive humans (7), have clearly shown that in vitro anti-CMV neutralizing activity does not necessarily confer protection.

(iv) With any of these prophylactic programs, it is clear that the addition of antilymphocyte antibody therapy—the immunosuppressing agents with the greatest ability to reactivate latent virus—to the antirejection regimen attenuates the efficacy of the prophylactic effort. Recently, Hibberd et al. (22, 24) have reported that the addition of antilymphocyte antibody therapy to standard cyclosporine-based immunosuppressive programs in seropositive renal allograft recipients increased the incidence of CMV disease five-fold. When ganciclovir was administered preemptively for the duration of the antilymphocyte antibody treatment (usually 10 to 14 days), the incidence of clinical disease fell from >50% to the baseline value of approximately 15%. In this instance, the antimicrobial strategy was tailored to meet the special challenge posed by the intensive immunosuppressive therapy required. We have found this approach to be equally effective in recipients of heart, liver, and lung allografts (24).

In sum, considerable progress has been made in both the treatment and, even more important, the prevention of CMV disease. Although this is an area of great flux at present, we speculate that the most effective anti-CMV strategy that emerges will have the following features: a basic prophylactic program given to all patients at risk for CMV disease; the prophylactic program will probably combine low doses of both an antiviral agent such as acyclovir or ganciclovir with low doses of an immunoglobulin preparation; in addition, preemptive therapy with ganciclovir will be added at times of optimal stress—during periods of intensive immunosuppression (as in the studies of Hibberd et al. [22, 24]) or when there are laboratory markers of early evidence of viral replication. Recently, it was shown in bone marrow transplant patients that the initiation of ganciclovir therapy when CMV was isolated on bronchoalveolar lavage (48) or from other bodily sites (particularly blood [19]) prior to the onset of clinical disease was quite effective in preventing the development of CMV pneumonia. With the advent of such techniques as direct CMV detection in buffy coat preparations by immunoflourescence (antigen detection [55]) or polymerase chain reaction (28), the possibility of a laboratory marker that can be used to trigger preemptive therapy while the infection is still at a subclinical stage appears quite feasible.

Such an approach to the prevention of CMV infection will have the added advantage of effectively preventing herpes simplex virus infection and may have benefits in the prevention of Epstein-Barr virus (EBV)-mediated disease as well (45). The clinical effects of EBV in the organ transplant

patient, like those of CMV, are quite broad. The critical effect, however, is its role in the pathogenesis of EBV-associated lymphoproliferative disease. EBV reactivates from latency and can be isolated from the oropharyngeal secretions of 20 to 30% of EBV-seropositive transplant patients, with this figure rising to 70 to 80% in patients receiving antilymphocyte antibody therapy. Secondary infection of B lymphocytes and subsequent immortalization occur. Normally, these infected, transformed B lymphocytes are eliminated by an effective surveillance system, the key elements of which are human leukocyte antigen-restricted, virus-specific, cytotoxic T cells. Cyclosporine, as well as other components of the immunosuppressive program, blocks this surveillance mechanism in a dose-related fashion and, hence, permits the processes that lead to lymphoproliferative disease to proceed (45). Patients, particularly children, with primary EBV infection posttransplantation have the highest risk for developing lymphoproliferative disease. Overall, however, since the vast majority of individuals receiving an organ transplant are EBV seropositive, the majority of cases of lymphoproliferative disease occur as a result of reactivation infection (39, 45). Preiksaitis et al. (39) have demonstrated that those patients who excrete the greatest amount of EBV in their oropharyngeal secretions posttransplantation (those with primary infection fall into this category) are at greatest risk of developing lymphoproliferative disease and that both acyclovir and ganciclovir are effective in significantly lowering the titer of EBV. Thus, it is not unreasonable to suggest that administration of preemptive antiviral therapy at times of increased immunosuppression will have benefits for EBV-seropositive as well as CMV-seropositive organ transplant patients.

ANTIMICROBIAL STRATEGIES AGAINST *PNEUMOCYSTIS CARINII*, *TOXOPLASMA GONDII*, AND STRONGYLOIDES STERCORALIS IN ORGAN TRANSPLANT RECIPIENTS

The incidence of *P. carinii* pneumonia in organ transplant patients receiving no antimicrobial prophylaxis is approximately 5 to 10% (21, 23, 25, 45). Treatment of such patients with high-dose trimethoprim-sulfamethoxazole or intravenous pentamidine is effective in more than 80% of individuals, but it is associated with a high rate of side effects. The most important of these side effects is severe nephrotoxicity caused by interactions with cyclosporine (see below) and bone marrow inhibition (45). In contrast, low-dose trimethoprim-sulfamethoxazole (e.g., 80 mg of trimethoprim plus 400 mg of sulfamethoxazole once daily) is both highly effective in preventing *Pneumocystis* pneumonia and is largely free of the toxic side effects that complicate full-dose therapeutic programs (23, 30, 45). In those patients who are unable to tolerate low-dose trimethoprim-sulfamethoxazole prophylaxis, alternative regimens such as monthly aerosolized or parenteral pentamidine (and, presumably, other regimens such as dapsone that are effective in patients with AIDS) are substituted. The exact duration of time that such prophylaxis should be continued is unclear. Since more than 80% of the cases of *P. carinii* infection occur in the first 6 months posttransplantation, our policy has been to prescribe prophylaxis for 6 months in renal transplant patients. This is continued for an additional 6 months in the extrarenal transplant patients and is reinstituted any time that the patient's level of immunosuppression is going to be increased for more than a few days (45).

In the special case of the heart transplant patient who is seronegative for toxoplasmosis prior to transplantation and receives an allograft from a toxoplasmosis-seropositive donor (and thus is at high risk for disseminated toxoplasmosis), pyrimethamine and sulfadiazine provide effective prophylaxis against both *P. carinii* and toxoplasmosis. Although there are scattered reports of toxoplasmosis in noncardiac organ transplant recipients, the incidence appears to be so low that routine antitoxoplasmosis prophylaxis for these patients does not appear to be indicated (16, 20, 27, 45).

S. stercoralis can cause life-threatening hyperinfestation syndromes or disseminated infection with accompanying gram-negative sepsis and/or meningitis in the transplant patient years after the individual acquired asymptomatic infection in areas endemic for *S. stercoralis* (e.g., much of the developing world). Whereas eradication of infection pretransplantation with thiobendazole is relatively easy, treatment of the life-threatening infections posttransplantation is difficult. Hence, examination of purged stool or small bowel samples from individuals with histories of exposure to this infectious agent is appropriate pretransplantation. Alternatively, preemptive therapy in anyone with an appropriate epidemiologic history is not unreasonable, particularly given the difficulties in diagnosing *S. stercoralis* infection (16, 35, 45).

ANTIMICROBIAL STRATEGIES AGAINST BACTERIAL INFECTION IN THE ORGAN TRANSPLANT RECIPIENT

Both low-dose trimethoprim-sulfamethoxazole and low-dose ciprofloxacin have clearly been shown to provide significant protection against the development of urinary tract infections in renal transplant recipients (18, 23, 57). In the case of trimethoprim-sulfamethoxazole, additional protection is also provided against clinical infections with such organisms as *Listeria monocytogenes*, *Nocardia asteroides*, and perhaps other bacterial pathogens, as well as the previously discussed *P. carinii* (45). Again, a 6- to 12-month period of prophylaxis posttransplantation appears to be adequate for preventing the majority of such infections.

Perioperative antibacterial administration has been shown to be effective in preventing wound infections in renal transplant recipients (45, 56, 58). In this instance, such therapy should be aimed at uropathogens and staphylococci. Such regimens as cefazolin, cefamandole, or ampicillin-sulbactam administered on an on-call basis in the operating room and continuing for less than 24 h posttransplantation have been quite effective (e.g., at our hospital, a wound infection rate of <0.2% has been observed over the past 10 years). Although no comparable controlled studies have been performed in patients undergoing extrarenal organ transplantation, perioperative prophylaxis has become standard practice. The general principles to be applied here, we believe, are the following. Eradicate the active infection prior to transplantation, perioperative prophylaxis should begin on an on-call basis in the operating room and should continue for less than 3 days posttransplantation, and the antibiotics chosen should be designed to cover staphylococci and the resident flora of the transplanted site (e.g., gram-negative organisms and, possibly, *Candida* species in the case of liver transplantation). In the case of lung transplant candidates, our practice has been to monitor their sputum cultures at least twice monthly prior to transplantation and then to individualize the prophylactic regimen to reflect the resident flora in the individual whose lung is being transplanted (45).

Liver transplantation, of all the forms of organ transplantation, has been associated with the highest rate of life-threatening bacterial and candidal infections, with major infections reported in as many as 79% of liver transplant patients. Most such infections are located intra-abdominally and are due to such factors as surgical manipulation of the bowel and biliary tree at the time of liver transplantation, devitalization of remaining tissues, intraperitoneal hemorrhage perioperatively, and the need for reexploration (6, 11, 38, 45, 60). Adapting the selective bowel decontamination approach used in cancer chemotherapy patients, a number of groups administer a variety of nonabsorbable antibacterial agents (e.g., gentamicin and polymyxin B combined with nystatin or amphotericin B) orally to eradicate the aerobic gram-negative flora while leaving the anaerobic flora, which confers colonization resistance, intact (34, 38, 59, 62). Although groups of investigators such as those at the Mayo Clinic (38, 61, 62) have reported excellent results with this approach, important questions remain. How much of the success is due to the antimicrobial program and how much is due to technically expert surgery; what is the relative efficacies of oral quinolones or trimethoprim-sulfamethoxazole in comparison with that of the nonabsorbable antimicrobial program (9); and, finally, are there subgroups of patients who merit greater or lesser amounts of therapy with the preemptive approach previously described for viral infection? In our own liver transplant program, prophylactic trimethoprim-sulfamethoxazole plus clotrimazole or nystatin therapy has been quite successful in decreasing the incidence of infection, provided that no anatomical abnormalities (i.e., hepatic infarction or bowel perforation) are present, and preemptive therapy with such drugs as vancomycin plus aztreonam or ampicillin-sulbactam is added whenever liver biopsy is performed or biliary tract manipulation is undertaken (colonization of the biliary tree posttransplantation with such organisms as *Staphylococcus epidermidis*, enterococci, and/or members of the family *Enterobacteriaceae* should be assumed). This last appears to be particularly important in patients whose biliary anastomosis is a choledochojejunostomy (5, 45). Without such prophylaxis, liver biopsy may be complicated by intrahepatic abscess formation and cholangiography may be complicated by cholangitis—all because of the manipulation of the colonized biliary tree.

ANTIMICROBIAL STRATEGIES AGAINST FUNGAL INFECTIONS IN ORGAN TRANSPLANT RECIPIENTS

The most common fungal infections that occur in organ transplant patients are those caused by *Candida* and *Aspergillus* species. Particular clinical syndromes of importance are candidal urinary tract infections in renal transplant recipients, particularly diabetics, because obstructing fungal balls can develop in these patients; intra-abdominal candidal infections in and around the liver in liver transplant patients; and invasive pulmonary aspergillosis in any transplant patient. Although well-controlled studies documenting efficacy are not available in organ transplant recipients, the following recommendations appear to be reasonable.

(i) Bowel decontamination for candidal species in liver transplant candidates and recipients appears to decrease the incidence of posttransplant candidal infection. Whether this is best accomplished with the nonabsorbable drugs nystatin or clotrimazole or with such systemic drugs as fluconazole remains to be determined (38, 45, 61, 62). In addition, some groups have advocated the use of a short (<2-week) course of intravenous amphotericin peritransplantation (34).

(ii) Preemptive therapy of asymptomatic candiduria is indicated, particularly in diabetic renal transplant patients. Because of toxicity issues, our current preference is for 2 weeks of fluconazole or low-dose (10 mg/day) amphotericin B plus flucytosine to accomplish this task (45).

(iii) Preemptive therapy of transplant patients whose respiratory tracts, either upper or lower, are colonized with *Aspergillus* species appears to be warranted. This appears to be particularly important in patients with cystic fibrosis who are ready to receive either a lung or a liver transplant. Whether amphotericin B or itraconazole is best suited for this task and the role that aerosolized amphotericin B can play here remains to be determined (45).

GENERAL PRINCIPLES OF ANTIMICROBIAL TREATMENT OF ESTABLISHED INFECTION IN ORGAN TRANSPLANT RECIPIENTS

Thus far in this minireview, preventive strategies have been stressed. An important reason for this is the potential toxicities of full-dose antimicrobial treatment regimens in patients receiving cyclosporine-based immunosuppressive regimens (the current standard of care in organ transplantation). Three types of interactions commonly occur between cyclosporine and a variety of antimicrobial agents. Certain drugs (most notably rifampin) upregulate the metabolism of cyclosporine by the critical hepatic cytochrome P-450 enzyme system, thus decreasing the levels of cyclosporine in blood and the immunosuppressing effect of cyclosporine and potentially leading to allograft rejection. Other drugs (most notably erythromycin and presumably the newer macrolides ketoconazole, itraconazole, and, to a lesser extent, fluconazole) downregulate the hepatic metabolism of cyclosporine, leading to higher levels of the drug in blood, and the potential for both cyclosporine toxicity and overimmunosuppression (some groups have advocated the routine administration of these antimicrobial agents to take advantage of this effect by lowering the dose and cost of cyclosporine required). Finally, there is non-dose-related, presumably idiosyncratic, synergistic nephrotoxicity. This last interaction is the one that is of primary concern, because the first two interactions can be dealt with by monitoring cyclosporine levels in blood and making appropriate dosage adjustments. Synergistic nephrotoxicity has been observed with an ever increasing list of antimicrobial compounds, most notably amphotericin B, aminoglycosides, vancomycin, high therapeutic doses of trimethoprim-sulfamethoxazole, pentamidine, and itraconazole. In general, antimicrobial therapy should emphasize the use of extended-spectrum beta-lactam molecules, quinolones (even here, higher doses may be of concern, because we have observed toxicity with doses of ciprofloxacin of >800 mg/day in transplant patients with normal renal function), and fluconazole. However, the general rule remains that when unexplained deterioration in renal function occurs in transplant patients, possible antimicrobial interactions with cyclosporine must be considered (45, 47).

SUMMARY

Since the early days of transplantation, infection has been a major consequence of antirejection immunosuppressive therapy. Increasingly effective prophylactic and preemptive strategies are being developed to prevent the infectious consequences of immunosuppressive therapy. Although the

data base is incomplete and there remains a compelling need for well-designed, randomized, comparative trials, the potential for controlling life-threatening viral, bacterial, fungal, and protozoal infections exists. The cornerstone of this effort is the recognition that effective immunosuppressive strategies require an antimicrobial program to make them safe and that such an antimicrobial program needs to be individualized in order to be appropriately matched with the needs of the antirejection program. Thus, escalation and de-escalation of the antimicrobial program should be carried out to match the immunosuppressive program. Infection and rejection remain closely intertwined, linked by the immunosuppressive program that is prescribed.

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