Infections and immunizations in organ transplant recipients: a preventive approach

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■ **BACKGROUND** Infections after organ transplantation can be devastating in immunocompromised patients.

■ **OBJECTIVE** To review strategies for preventing infections after transplantation.

■ **SUMMARY** Immunization remains a cornerstone of preventive practice, but the suboptimal response to vaccinations in patients receiving immunosuppressive therapy presents an ongoing challenge. More work is needed to determine which of the numerous strategies for preventing symptomatic cytomegalovirus infection is most effective and economical, and under which circumstances. Prevention of *Pneumocystis carinii* pneumonia remains an important issue, especially in sulfa-intolerant patients. The relationship between different immunosuppressive programs and occurrence of infectious complications such as lymphoproliferative disease is just beginning to be understood. The toxicity of amphotericin B in this population has led to a search for more effective means of preventing and treating fungal infections. Finally, a new set of possible pathogens (such as the recently recognized human herpesvirus-6) is on the horizon.

■ **CONCLUSIONS** The best preventive approach encompasses awareness of epidemiologic risk, early detection of infection, appropriate prophylactic or preemptive therapy for specific infections, and close collaboration between the infectious-disease clinician and the transplant team.

■ INDEX TERMS: OPPORTUNISTIC INFECTIONS; TRANSPLANTATION; CYTOMEGALOVIRUS; *PNEUMOCYSTIS CARINII* PNEUMONIA ■ CLEVE CLIN J MED 1994; 61:386–392

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BECAUSE OF the severity of many infectious disease syndromes in immunosuppressed organ transplant recipients, a variety of preventive strategies have been devised to address major infections that have posed difficult treatment problems in the past. These strategies have succeeded in transforming the first weeks after transplantation into a time in which preventing infection, rather than watchful waiting, is a major focus. Many challenges remain, however, as a number of potentially devastating infectious complications still occur despite the most careful prophylactic programs.[1]

This brief discussion will present a practical review of some of the current literature addressing these problems. This is by no means a complete overview; topics such as hepatitis B and C, postoperative bacterial infections, parasitic infections, respiratory viruses, and mycobacterial infections have been omitted. For more in-depth analyses of these and other issues pertaining to infectious disease and transplantation, the reader is referred to the writings of Dr. Robert Rubin and colleagues,[2–6] the inspiration for many of the ideas presented herein.

IMMUNIZATIONS

The issue of immunization, both before and after transplantation, has been recently reviewed by Hibberd and Rubin,[1] who have summarized current recommendations and literature. General principles involve avoiding live-virus vaccines, giving certain vaccines despite the possibility of limited efficacy, and recognizing that immunization is part of an overall program that also includes prophylactic or preemptive therapy or both in situations of acute exposure.[5]

Studies have documented variable response to influenza vaccine, but it is still recommended yearly. Amantadine may be considered at times of severe influenza outbreaks in the community. Pneumococcal vaccination produces a rise in titer in most transplant recipients, but antibody levels may decline, and some experts suggest repeating vaccination every 2 to 5 years. Measles-mumps-rubella vaccine and oral polio vaccine are live-virus vaccines and should be avoided. In addition, family members of transplant recipients should receive inactivated rather than oral polio vaccine, as the vaccine strain can be transmitted to household contacts.

The potentially severe complications of hepatitis B in organ transplant recipients are well known. Vaccination is recommended if a transplant recipient is seronegative; however, serologic response is disappointing, ranging from 18% to 32% in renal transplant recipients. Patients who are uremic before transplantation also have a suboptimal response. If possible, the best time to vaccinate is before the onset of end-stage disease. More research is needed concerning strategies such as adjuvants to boost the response to existing vaccines.[7]

The tetanus-diphtheria booster is controversial. Anecdotal evidence links this vaccine with organ rejection; therefore, some prefer to give it before transplantation and to treat tetanus-prone wounds after transplantation with tetanus immune globulin alone.[1]

PROPHYLACTIC MEASURES AFTER EXPOSURE

Another category of prophylactic measures relates to exposure. Primary varicella infection can be devastating in immunocompromised transplant recipients.[8] Susceptible patients exposed to varicella should receive varicella-zoster immune globulin as soon as possible and should be observed closely for the earliest sign of clinical disease (which should be promptly treated with high-dose acyclovir if it occurs). In this population, cutaneous manifestations of varicella may be attenuated, especially when varicella-zoster immune globulin is administered, and the clinician should be alert for a predominantly visceral presentation. The role of the varicella vaccine has yet to be defined in this population, but it is potentially very useful.

As mentioned above, amantadine may be useful in exposure to influenza A. Some also recommend immunoglobulin prophylaxis for recent measles exposure in susceptible patients, but, ideally, measles-mumps-rubella vaccine should be administered before transplantation.

The importance of an infectious-disease evaluation before transplantation cannot be overemphasized, particularly for patients from high-risk endemic areas for certain diseases. Miliary tuberculosis and disseminated strongyloidiasis have occurred in the setting of immunosuppression after transplantation. When possible, screening and appropriate therapy for these and other infections should be instituted before transplantation. A positive purified protein derivative skin test before transplantation, regardless of the timing of conversion, should prompt consideration of prophylaxis, as both active tuberculosis and the multiple-drug regimens required to treat it can cause serious problems for transplant recipients.

Preventing infectious diseases is all the more important in light of the multiple interactions between antimicrobial agents and cyclosporine.[2–4] Rifampin and, to a lesser extent, isoniazid can lead to increased metabolism of cyclosporine, resulting in lower levels and possible rejection. On the other hand, a number of agents such as the azole antifungals (especially ketoconazole) and macrolides (especially erythromycin) can raise cyclosporine levels, leading to potential toxicity and increased immunosuppression. Many antimicrobials have been found in some cases to cause synergistic nephrotoxicity when given with cyclosporine; these include aminoglycosides, amphotericin B, and, less commonly, trimethoprim-sulfamethoxazole and the azoles. Given these potential difficulties, any preventive measures that avert the need for lengthy therapy for a full-blown infectious syndrome will be beneficial.

Rubin[2–5] has delineated the distinction between prophylactic and preemptive therapy in this patient population. Both are important components of an

overall strategy. Prophylactic therapy is the institution of pharmacologic or immunologic measures or both to all patients in order to prevent infections for which this group is at high risk (ie, acyclovir to prevent herpes simplex infection or trimethoprim-sulfamethoxazole to prevent *P carinii* pneumonia in the first months after transplantation). Preemptive therapy, on the other hand, is the early use of a therapeutic measure, based on some indicator of early infection or particular risk factor in a subgroup of patients to avert development of more serious disease. Such situations might include treating a subclinical cytomegalovirus (CMV) infection detected by the CMV antigenemia assay or polymerase chain reaction (see below) before the full-blown CMV syndrome develops or promptly treating asymptomatic candiduria to prevent upper-urinary tract infection or other invasive disease.

CYTOMEGALOVIRUS INFECTION

CMV shares with other viruses in the herpesvirus family the ability to remain latent after primary infection and to reactivate in the setting of immunosuppression. The risk of acquiring symptomatic CMV infection after transplantation varies from approximately 60% for primary infection (when a seronegative recipient receives an organ from a seropositive donor) to 20% to 40% for reactivation of a previous infection or superinfection with a new strain of CMV in a previously seropositive recipient.[2,9] In the timetable of infection after transplantation, the greatest risk for symptomatic CMV infection occurs from 1 to 4 months after transplantation.[3] At this time, the virus may cause fever, leukopenia, hepatitis, pneumonitis, gastrointestinal lesions, and other direct manifestations. Later, CMV infection may be manifested as retinitis. In addition, CMV infection has a number of indirect effects in transplant recipients,[6] including a deleterious effect on the immune system that consequently increases the risk for opportunistic infections such as *P carinii* pneumonia and aspergillosis. There is also a suggested link to allograft injury, either by up-regulation of major histocompatibility complex antigens or by molecular mimicry.[4]

For these reasons, preventing CMV disease has been the target of intensive study. Different immunosuppressive regimens appear to have significantly different effects on risk for development of CMV infection. The antilymphocyte therapies muromonab-CD3 (OKT3) and antithymocyte globulin (ATG) appear to be powerful reactivators of CMV, whereas cyclosporine blocks the specific cytotoxic T-cell response to the virus and facilitates its replication once reactivation has occurred.[4] Hibberd et al[10] found that OKT3 administration increased the risk of CMV disease fivefold, particularly in seropositive renal transplant recipients. A prophylactic course of ganciclovir given during a course of OKT3 or ATG, however, decreased the CMV risk to baseline.[11] At many centers, it is now established practice to use such courses of ganciclovir at times of increased immunosuppression, particularly with OKT3 or ATG.

Prophylaxis of CMV infection remains a controversial issue. Only a few representative studies from a huge literature will be mentioned here. A number of regimens have been shown to have some efficacy in preventing CMV disease after transplantation: these include high-dose oral acyclovir, CMV hyperimmune globulin (CMVIG), standard unselected immunoglobulin (IVIG), and ganciclovir.

Clinical trials of CMV prevention

Balfour et al[12] showed a reduction in symptomatic CMV disease in renal transplant recipients, including a benefit in prevention of primary infection, with high-dose oral acyclovir. Benefit has been more difficult to demonstrate in other organ transplant recipients, though one study in liver recipients showed a benefit in a small group of patients.[13]

Snydman et al[14] studied CMVIG for prevention of symptomatic primary CMV in renal transplant patients and found that there was a significant degree of protection (21% of the CMVIG group developed CMV-associated syndromes vs 60% of the control group) and also an associated reduction in fungal and parasitic opportunistic infections. The more recent study by Snydman et al[15] examining the utility of prophylactic CMVIG in liver transplant recipients showed a less striking reduction in severe CMV disease, and no protection in primary infection.

Standard immunoglobulin has also been studied in renal transplant patients; Steinmuller et al[16] found a 26% rate of febrile illness attributed to CMV in patients receiving IVIG prophylaxis as compared with 63% of historical controls. Regimens based on prophylactic ganciclovir have gained momentum from the work of Merigan et al,[17] employing a 28-day course of ganciclovir after heart transplantation. CMV illness decreased from 46% in

controls to 9% in ganciclovir recipients, but this regimen did not prevent primary infection.

Few trials have compared different modalities of prevention head-to-head. Martin et al[18] conducted a randomized trial of sequential ganciclovir plus high-dose oral acyclovir vs high-dose oral acyclovir alone in liver transplant recipients. Ganciclovir was given for 2 weeks, and the total period of prophylaxis was 3 months. Symptomatic CMV infection occurred in 28% of acyclovir recipients and in 9% of patients receiving the ganciclovir-containing regimen. This effect was seen primarily in seropositive recipients; neither treatment regimen had an effect on the incidence of primary infection, though ganciclovir may have ameliorated the manifestations of primary infection.

There are also several studies of combination regimens. Stratta et al[19] studied IVIG and acyclovir in liver transplant recipients and found a benefit compared with historical untreated controls. Nicol et al[20] found a similar benefit with CMVIG and low-dose acyclovir in renal transplant recipients at risk for primary disease. Nakazato et al[21] compared IVIG plus acyclovir vs IVIG plus ganciclovir in liver recipients and found a 15% vs 3.8% incidence of symptomatic CMV, though only a small number at risk for primary infection were included. Different organ transplant settings may require different prophylactic strategies: Bailey et al[22] demonstrated the failure of 10 to 21 days of ganciclovir plus IVIG in a small number of lung transplant patients.

Current topics in CMV research

Other topics of current interest include new methods for early detection of CMV in the presymptomatic phase. These include the CMV antigenemia assay, which detects the matrix protein pp65 in peripheral blood leukocytes,[23] and the polymerase chain reaction.[24] It is hoped that prevention or amelioration of CMV-related syndromes may be possible by utilizing these assays to detect early infection or reactivation of the virus.[25]

The subject of CMV-negative blood or leukocyte-filtered blood is also an important one, but the indications for and cost-effectiveness of administration to various subgroups of transplant recipients are still matters for discussion. Considerations include the risk not only of CMV primary infection but also superinfection (suggesting that seropositive as well as seronegative recipients may benefit from such selective blood administration). In addition, the issue of preventing leukocyte-associated infections other than CMV raises the question of an advantage to leukocyte-filtered over CMV-negative blood, though the former is more expensive.

Conclusions

Several conclusions regarding an effective prophylactic regimen are warranted. Most studies to date have involved a comparison of a single preventive regimen and placebo. More work is needed to evaluate combination regimens and to compare existing preventive modalities head-to-head in randomized trials. Cost-effectiveness is also an issue; Tsevat et al[26] have analyzed the cost-effectiveness of CMVIG, and similar analyses for other modalities will be important. Whatever modality is used, the addition of acyclovir (at times when ganciclovir is not being used) will prevent serious herpes simplex virus infection; thus, most regimens involve prophylactic (at least low-dose) acyclovir as a component, either from the time of transplantation or after a course of ganciclovir. One possible regimen may be a combination of a globulin preparation with an antiviral agent, with addition of ganciclovir (if not already included) during administration of OKT3 or ATG.[4] Newer antiviral agents, when available for testing, will also be of interest.

PNEUMOCYSTIS CARINII PNEUMONIA

Standard therapy for full-blown *P carinii* pneumonia (high-dose trimethoprim-sulfamethoxazole, intravenous pentamidine) is often toxic in transplant recipients because of synergistic nephrotoxicity with cyclosporine and other adverse effects.[2] Prevention is far preferable and can be achieved with low-dose oral trimethoprim-sulfamethoxazole in patients who tolerate it.[2,27–29] This is also effective prophylaxis for urinary tract infection and probably for *Listeria* and *Nocardia* as well.[3] Patients not receiving prophylaxis specifically directed at *P carinii* pneumonia have at least a 10% risk of developing this infection, as in a group of patients who received ciprofloxacin prophylaxis for urinary tract infection after transplantation.[30]

Prophylaxis in sulfa-intolerant patients is difficult. Monthly administration of aerosolized pentamidine has often been employed, but is incompletely effective and may raise infection-control issues such as spread of undetected tuberculosis. Trials of newer anti-*Pneumocystis* agents will be of in-

terest. Prophylaxis should be continued for 6 months after renal transplantation and for a longer period in patients with other organ transplants, chronic rejection, CMV infection (because of its immunosuppressive effect), or who have required more than the usual doses of immunosuppressive medication.[2]

EPSTEIN-BARR VIRUS-RELATED LYMPHOPROLIFERATIVE DISEASE

Lymphoproliferative disease is a significant cause of morbidity and mortality in transplant recipients, especially those that have received antilymphocyte therapies.[31,32] The spectrum of lymphoproliferative disease after transplantation ranges from a mononucleosis-like illness to high-grade B-cell lymphoma, and from polyclonal to monoclonal on pathologic examination. The process is often multicentric and may involve the central nervous system, gastrointestinal tract (with bleeding and perforation), liver, spleen, lymph nodes, allograft, and many other organs.[33] The disease may present as a febrile syndrome with few localizing signs, which makes differentiation from other processes initially difficult.

The pathogenesis involves Epstein-Barr virus replication, which is often driven by OKT3 or ATG, followed by cyclosporine-induced inhibition of virus-specific cytotoxic T lymphocytes that normally keep Epstein-Barr virus-infected, transformed B cells in check.[4] Swinnen et al[34] found a markedly increased incidence among heart transplant recipients receiving OKT3, and the effect was dose-related.

Efforts at prevention have been furthered by recent work by Preiksaitis et al,[35] who demonstrated that high-level Epstein-Barr virus shedding in the oropharynx correlated with primary infection, OKT3 administration, and high-dose steroids, and was associated with the subsequent development of lymphoproliferative disease. This shedding was inhibited by both acyclovir and ganciclovir, suggesting that antiviral therapy might be most useful early, ie, when levels of viral replication are still low. Whether clinically significant degrees of protection might be achieved with such an antiviral strategy still remains to be demonstrated. Basgoz et al[36] also found a significant association with CMV infection.

As treatment has generally been disappointing, with the exception of drastic reductions in immunosuppression, the search for preventive strategies has intensified. Because of its association with CMV,[36] Epstein-Barr virus should be considered in the evaluation of preventive strategies for CMV, and as newer CMV-directed antiviral agents emerge, their activity against Epstein-Barr virus will be important to evaluate. The activity of various globulin preparations in the prevention of primary Epstein-Barr virus infection would also be of interest.

FUNGAL INFECTIONS

Fungal infections remain a greatly feared complication after transplantation. These include candidiasis, cryptococcosis, aspergillosis, the endemic mycoses (histoplasmosis, blastomycosis, and coccidioidomycosis), and more unusual fungi. In the past, when amphotericin B was the only effective therapy, nephrotoxicity was a major problem. Though amphotericin B remains standard therapy for many conditions, the newer antifungal agents, particularly the azoles, have become increasingly useful for prophylaxis as well as for treating established infections.

The azole agents include ketoconazole, fluconazole, and itraconazole, of which the last two have become particularly widely used in transplant recipients.[37] They are generally well tolerated, but cyclosporine levels may increase and should be monitored, as should liver function. Fluconazole is effective against most *Candida* (except *Candida krusei* and *Torulopsis*) and is useful for mild-to-moderate candidal infection, including asymptomatic candiduria, which can lead to severe complications in this population.[4] Fluconazole is also effective in subacute cryptococcal disease.

For severe candidal or cryptococcal disease, amphotericin B is often used in the acute setting, followed by fluconazole maintenance therapy. Itraconazole has activity against *Aspergillus* species, and is seeing increasing use in the setting of *Aspergillus* respiratory colonization for prevention of invasive disease. This use has yet to be supported by controlled data, however. Itraconazole may also be useful in certain clinical situations involving endemic mycoses or the rare amphotericin-resistant fungi. Newer preparations such as liposomal amphotericin B have yet to be fully tested as therapy or prophylaxis in this population.

Given the substantial risk of fungal infection, meticulous attention to prevention is crucial. Mucosal yeast prophylaxis should be universally administered for at least several months after transplanta-

tion. Early removal of foreign bodies such as urinary catheters will discourage fungal colonization. Recognition of potential nosocomial exposures, such as the well-documented association of hospital construction and aspergillosis,[38] should result in preventive measures such as masks for off-floor transport, especially in areas of increased risk. In addition, chronic allograft dysfunction and heavy immunosuppression coupled with other opportunistic infections should alert the clinician to the patient who is at particular risk for fungal infection and who may need prophylactic measures continued longer and more vigorously than others.

FRONTIERS OF PREVENTION: NEWER INFECTIOUS AGENTS

As preventive strategies evolve, they must take into account the ever-expanding knowledge base of infectious syndromes after transplantation. Human herpesvirus-6 (HHV-6) is an example of a pathogen that may assume increasing importance in this population as it is better understood. Its clinical description is evolving and includes roseola or exanthem subitum in infants, a mononucleosis-like syndrome in primary infection in adults, and various possible clinical syndromes that have been cited as reactivation in the setting of immunosuppression after transplantation.[39] It has been suggested that this CMV-like virus may be the cause of some cases of interstitial pneumonitis after bone marrow transplantation,[40,41] and it has been linked to possible rejection in renal transplant patients.[42]

In the era of the HIV pandemic, the HIV virus and associated pathogens pose a risk to transplant recipients that is beyond the scope of this discussion. Similarly, with the rise of multi-drug-resistant tuberculosis, new issues in prevention will likely arise in the future, including the troublesome interactions of some antituberculous drugs with immunosuppressive agents. The presence in hospitals of highly antibiotic-resistant, nosocomially transmitted bacterial strains (*Enterococcus*, gram-negative bacilli) poses a considerable problem that transcends the field of transplantation.

Thus, many challenges remain despite considerable progress in preventing infection after transplantation. Ultimately, the refinement of immunosuppressive therapy, ideally with the ability to preserve some capacity for pathogen-specific immune responsiveness while still preventing rejection, will be of paramount importance. Until (and even after) this is achieved, a broad preventive approach that encompasses awareness of epidemiologic risk, early detection of infection, appropriate prophylactic or preemptive therapy for specific infections, and close collaboration between the infectious-disease clinician and the transplant team offers the best chance for steering a clear course in the first months after transplantation.

REFERENCES

1. **Hibberd PL, Rubin RH.** Approach to immunization in the immunosuppressed host. Infect Dis Clin North Am 1990; **4:**123–142.
2. **Rubin RH, Tolkoff-Rubin NE.** Antimicrobial strategies in the care of organ transplant recipients. Antimicrob Agents Chemother 1993; **37:**619–624.
3. **Rubin RH.** Infection in the organ transplant patient. In: Rubin RH, Young LS, editors. Clinical approach to infection in the compromised host. 3rd ed. New York: Plenum Medical Book Company, in press.
4. **Rubin RH.** Infectious disease complications of renal transplantation. Kidney Int 1993; **44:**221–236.
5. **Rubin RH.** Preemptive therapy in immunocompromised hosts [editorial]. N Engl J Med 1991; **324:**1057–1058.
6. **Rubin RH.** Impact of cytomegalovirus infection on organ transplant recipients. Rev Infect Dis 1990; **12(Suppl 7):**S754–S766.
7. **Hibberd PL, Rubin RH.** Immunization strategies for the immunocompromised host—the need for immunoadjuvants [editorial]. Ann Intern Med 1989; **110:**955–956.
8. **Lynfield R, Herrin JT, Rubin RH.** Varicella in pediatric renal transplant recipients. Pediatrics 1992; **90:**216–220.
9. **Chou S.** Neutralizing antibody responses to reinfecting strains of cytomegalovirus in transplant recipients. J Infect Dis 1989; **160:**16–21.
10. **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:**68–72.
11. **Hibberd PL, Tolkoff-Rubin NE, Doran M, et al.** Preemptive therapy with ganciclovir during OKT3 administration—a promising strategy for prevention of symptomatic cytomegalovirus (CMV) disease in liver and heart transplant recipients. Abstract 57, p. 125. 11th Annual Meeting of the American Society of Transplant Physicians, 1992.
12. **Balfour HH Jr, Chace BA, Stapleton JT, Simmons RL, Fryd DS.** A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N Engl J Med 1989; **320:**1381–1387.
13. **Mollison LC, Richards MJ, Johnson PDR, et al.** High-dose oral acyclovir reduces the incidence of cytomegalovirus infection in liver transplant recipients. J Infect Dis 1993; **168:**721–724.
14. **Snydman DR, Werner BG, Heinze-Lacey B, et al.** Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal-transplant recipients. N Engl J Med 1987; **317:**1049–1054.
15. **Snydman DR, Werner BG, Dougherty NN, et al.** Cytomegalovirus immune globulin prophylaxis in liver transplantation: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1993; **119:**984–991.

16. **Steinmuller DR, Graneto D, Swift C, et al.** Use of intravenous immunoglobulin prophylaxis for primary cytomegalovirus infection post living-related donor renal transplantation. Transplant Proc 1989; **21**:2069–2071.
17. **Merigan TC, Renlund DG, Keay S, et al.** A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med 1992; **326**:1182–1186.
18. **Martin M.** Antiviral prophylaxis for CMV infection in liver transplantation. Transplant Proc 1993; **25(Supp 4)**:10–14.
19. **Stratta RJ, Shaefer MS, Cushing KA, et al.** A randomized, prospective trial of acyclovir and immune globulin prophylaxis in liver transplant recipients receiving OKT3 therapy. Arch Surg 1992; **127**:55–64.
20. **Nicol DL, MacDonald AS, Belitsky P, et al.** Reduction by combination prophylactic therapy with CMV hyperimmune globulin and acyclovir of the risk of primary CMV disease in renal transplant recipients. Transplantation 1993; **55**:841–846.
21. **Nakazato P, Burns W, Moore P, et al.** Viral prophylaxis in hepatic transplantation: preliminary report of a randomized trial of acyclovir and ganciclovir. Transplant Proc 1993; **25**:1935–1937.
22. **Bailey TC, Trulock EP, Ettenger NA, et al.** Failure of prophylactic ganciclovir to prevent cytomegalovirus disease in recipients of lung transplants. J Infect Dis 1992; **165**:548–552.
23. **van der Bij W, van Son WJ, van der Berg APM, et al.** Cytomegalovirus (CMV) antigenemia: rapid diagnosis and relationship with CMV-associated clinical syndromes in renal allograft recipients. Transplant Proc 1989; **21**:2061–2064.
24. **Hsia K, Spector DH, Lawrie J, Spector SA.** Enzymatic amplification of human cytomegalovirus sequences by polymerase chain reaction. J Clin Microbiol 1989; **27**:1802–1809.
25. **The TH, van den Berg AP, van Son WJ, et al.** Monitoring for cytomegalovirus after organ transplantation: a clinical perspective. Transplant Proc 1993; **25(Supp 4)**:5–9.
26. **Tsevat J, Snydman DR, Pauker SG, et al.** Which renal transplant patients should receive cytomegalovirus immune globulin? A cost-effectiveness analysis. Transplantation 1991; **52**:259–265.
27. **Kramer MR, Stoehr C, Lewiston NJ, Starnes VA, Theodore J.** Trimethoprim-sulfamethoxazole prophylaxis for Pneumocystis carinii infections in heart-lung and lung transplantation - how effective and for how long? Transplantation 1992; **53**:586–589.
28. **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**:255–274.
29. **Higgins RM, Bloom SL, Hopkin JM, Morris PJ.** The risks and benefits of low-dose cotrimoxazole prophylaxis for Pneumocystis pneumonia in renal transplantation. Transplantation 1989; **47**:558–560.
30. **Hibberd PL, Tolkoff-Rubin NE, Doran M, et al.** Trimethoprim-sulfamethoxazole compared with ciprofloxacin for the prevention of urinary tract infection in renal transplant recipients: a double-blind, randomized controlled trial. Online J Curr Clin Trials, August 11, 1992 (Doc. No. 15).
31. **Cockfield SM, Preiksaitis JK, Jewell LD, Parfrey NA.** Post-transplant lymphoproliferative disorder in renal allograft recipients. Transplantation 1993; **56**:88–96.
32. **Cohen JI.** Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. Medicine 1991; **70**:137–160.
33. **Nalesnik MA, Jaffe R, Starzl TE, et al.** The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. Am J Pathol 1988; **133**:173–192.
34. **Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al.** Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990; **323**:1723–1728.
35. **Preiksaitis JK, Diaz-Mitoma F, Mirzayans F, Roberts S, Tyrrell DLJ.** Quantitative oropharyngeal Epstein-Barr virus shedding in renal and cardiac transplant recipients: relationship to immunosuppressive therapy, serological responses, and the risk of post-transplant lymphoproliferative disorder. J Infect Dis 1992; **166**:986–994.
36. **Basgoz N, Hibberd PL, Tolkoff-Rubin N, Cosimi AB, Rubin RH.** Abstract No. P-1-50, 12th Annual Meeting of the American Society of Transplant Physicians, 1993.
37. **Conti DJ, Tolkoff-Rubin NE, Baker GP Jr et al.** Successful treatment of invasive fungal infection with fluconazole in organ transplant recipients. Transplantation 1989; **48**:692–695.
38. **Rubin RH.** The compromised host as sentinel chicken [editorial]. N Engl J Med 1987; **317**:1151–1153.
39. **Oren H, Sobel JD.** HHV-6: review. J Infect Dis 1992; **14**:741–746.
40. **Carrigan DR, Drobyski WR, Russler SK, et al.** Interstitial pneumonitis associated with HHV-6 after marrow transplantation. Lancet 1991; **338**:147–9.
41. **Cone R, Hackman RC, Huang M-LW, et al.** Human herpesvirus 6 in lung tissue from patients with pneumonitis after bone marrow transplantation. N Engl J Med 1993; **329**:156–161.
42. **Okuno T, Higashi K, Shiraki K, et al.** HHV-6 infection in renal transplantation. Transplantation 1990; **49**:519–522.