Review Article

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Management of Opportunistic Infections after Organ Transplantation

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Solid organ transplantation is a therapeutic option for end-stage organ diseases. However, complications including infection and graft rejection, which are related to immunosuppressive therapy, remain the major causes of morbidity and mortality following solid organ transplantation. The optimal approach to infection in solid organ transplant recipients is prevention; failing this, prompt and aggressive diagnosis and therapy are essential. In addition, the epidemiology of infections after solid organ transplantation has shifted as a result of changes in immunosuppressive strategies and improved survival. Immunosuppression must be linked with appropriate vaccinations, donor and recipient screening, patient education regarding infectious risks and lifestyle, monitoring, and antimicrobial prophylaxis.

Key Words: Organ transplantation, Infection, Immunosuppression
중심 단어: 장기이식, 감염, 면역억제

INTRODUCTION

Solid organ transplantation is a therapeutic option for end-stage organ diseases. Liver, kidney, heart, and lung transplantations have become the standard therapy for selected end-stage diseases. However, complications such as infection and graft rejection, which are related to immunosuppressive therapy, remain the major causes of morbidity and mortality following solid organ transplantation.

The host response is also less effective because of the mismatch in major histocompatibility antigens between the organ donor and host, which reduces the efficacy of direct pathway antiviral cellular immune responses. These factors render the allograft susceptible to invasive viral infection.

There are 3 general timeframes during which different common pathogens cause infectious diseases.

Most infections occurring during the first month after transplantation are related to surgery and postoperative hospitalization, including surgical site, lung, urinary tract, and indwelling device infections, and they are similar to those occurring in general surgical patients. After the first month, opportunistic infections begin to appear because of immunosuppression and immunomodulating viral infections such as cytomegalovirus (CMV) infection. Beyond the six months after transplantation, most patients have good transplant outcome and receive minimal immunosuppression, suffer from infections similar to those of the general population. Patients requiring high immunosuppression owing to recurrent acute or chronic rejection remain at risk of opportunistic infections classically observed during the second to sixth month after transplantation. Moreover, some patients may experience chronic viral infections such as hepatitis B or C, CMV, Epstein-Barr virus, or BK virus infection.

The optimal approach to infection in solid organ transplant recipients is prevention; failing this, its prompt and aggressive diagnosis and therapy are essential.

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BACTERIAL INFECTION

1. *Clostridium difficile*

Clostridium difficile is known to produce protein endotoxins that cause colonic mucosal inflammation and injury. This infection may present as diversely as fever, abdominal pain, and diarrhea. Antimicrobial therapy is a well-known risk factor for *C. difficile* infection.

In a retrospective study of 1932 kidney and kidney-pancreas transplantation patients, the overall incidence of *C. difficile* colitis was 8%, compared to 1~4% in the general surgery population(1).

In out setting, immunosuppression itself does not appear to increase *C. difficile* infection in kidney transplant patients(2).

Metronidazole 250~500 mg orally 3~4 times daily for 10~14 days is considered the treatment of choice. If patients fail to respond to metronidazole, vancomycin 125 mg orally 4 times daily for 10~14 days may be useful. Concerns about increased vancomycin resistance in other pathogens, such as enterococci, further discourage the use of oral vancomycin as the first-line therapy for *C. difficile* infection.

2. *Mycobacterium tuberculosis*

Latent tuberculosis (TB) infection can be reactivated because of immunosuppression. The infection may also be acquired from donors. Most transplant centers screen for TB infection preoperatively(3,4).

Treatmentof TB infection is not simple, particularly when combined with immunosuppressive therapy. Drug interactions create unique challenges, for example, cyclosporine, sirolimus, and tacrolimus are all substrates of cytochrome p450-3A isoenzymes, and a significant dose increase of these immunosuppressive agents may be necessary to maintain the therapeutic drug concentrations in the presence of rifampin(5,6).

VIRAL INFECTION

1. Cytomegalovirus (CMV)

Human cytomegalovirus or human herpesvirus 5 (CMV) belongs to the order Herpesvirales, family Herpesviridae, subfamily Betaherpesvirinae, genus Cytomegalovirus, and species Human herpesvirus 5(7). Symptomatic CMV infection occurs in 20~60% of all transplant recipients and is a significant cause of increased morbidity and mortality in this population(8,9). Compared with other organ transplant recipients, renal transplant patients are at a lower risk of CMV infection, in part owing to the lower burden of latent virus in renal allografts. The incidence of CMV infection in the renal transplant population is estimated to be between 8% and 32%(10,11). Serologic screening for antibodies to CMV should be performed in both donors and recipients before transplantation to identify patients who are at a risk of post-transplant infection and who might benefit from preventive strategies(12). Two strategies are commonly used for CMV infection prevention: (1) universal prophylaxis and (2) preemptive therapy. Universal prophylaxis involves giving antiviral therapy to all "at-risk" patients beginning at or immediately after transplantation for a defined time period. In preemptive therapy, patients are monitored at regular intervals for early evidence of CMV replication prior to the onset of clinical symptoms by using a laboratory assay(13). Patients with early replication are then treated with antiviral therapy to prevent symptomatic disease. Each approach has its advantages and disadvantages that must be considered in the context of the patient and the allograft(14). Preemptive therapy may decrease drug costs and toxicity. However, it requires excellent logistic coordination in order to obtain, receive, and act on results in a timely fashion; this can be difficult if patients live quite some distance from the transplant center. Prophylaxis might have the theoretical advantage of preventing reactivation of other viruses, such as human herpesvirus6 (HHV-6), and may be theoretically more likely to prevent the indirect effects of CMV infection. CMV resistance has been observed with both strategies. Drugs that have been evaluated for universal prophylaxis include acyclovir, ganciclovir, valacyclovir, valganciclovir, and immunoglobulin preparations. Based on current data, the optimal preemptive strategy is unknown. Preemptive therapy is well suited for transplant recipients at a low or intermediate risk of CMV disease, while prophylaxis may be better suited for those at a high risk(15,16). Some studies have concluded that preemptive valganciclovir therapy and valacyclovir prophylaxis are equally effective in preventing CMV disease after renal transplantation and

there is no difference in the overall costs between the two treatments(17,18). The same conclusions were obtained in studies using ganciclovir as the antiviral drug(19). A meta-analysis of 32 trials (3737 patients) performed to compare the outcomes of various prophylactic antivirals in transplant patients at risk of CMV disease demonstrated that prophylaxis decreased CMV disease, CMV infection, and all-cause mortality(20). This meta-analysis showed that ganciclovir was more effective than acyclovir in preventing CMV disease. Valganciclovir and intravenous ganciclovir were found to be as effective as oral ganciclovir for prophylaxis. However, ganciclovir use may be associated with a greater rate of CMV resistance than valganciclovir use, at least in the highest-risk recipients(21,22). The length of prophylactic treatment varies by institution but generally lasts for a minimum of 3 months.

Treatment of active CMV disease requires a combination of immunomodulation, antiviral therapy, and reduction of immunosuppression, if possible. The standard of care for treating CMV disease is 2~3 weeks of intravenous ganciclovir (5 mg/kg twice daily, dose adjustments for renal dysfunction) with demonstration of clinical and virological responses to therapy. In contrast, oral ganciclovir should not be used to treat CMV disease because of the limited absorption and poor bioavailability. In seronegative patients and those with a slow response to therapy, the addition of CMV hyperimmune globulin (100~150 mg/kg per dose intravenously, administered monthly) may be useful(23). More recently, the introduction of valganciclovir has made possible the oral treatment of CMV disease in solid organ transplant recipients. In a trial of 21 renal transplant recipients who had symptomatic CMV disease and viremia and were treated with valganciclovir, all patients cleared their infection and none experienced relapse during a mean follow-up of 5.5 months(24). Recently, a multicenter randomized controlled trial of 321 solid organ transplant recipients demonstrated that oral valganciclovir was not inferior to intravenous ganciclovir in the initial treatment of CMV viremia(25). Indeed, valganciclovir was recently shown to be as effective as intravenous ganciclovir in the treatment of mild-to-moderate (i.e., nonsevere) CMV disease(26). The duration of treatment for CMV disease should be individualized and guided by virological and clinical surveillance. Viremia should be cleared before therapy is discontinued in order to reduce the risk of clinical relapse. Previous studies have shown that persistent viremia at the end of therapy is associated with a higher risk of disease relapse(27). Alternative therapies (not Food and Drug Administration-approved for use in solid organ transplant recipients) include the use of foscarnet, cidofovir, and leflunomide; these are reserved for treatment of antiviral resistance. Foscarnet is active against most ganciclovir-resistant strains of CMV but has neurotoxicity and renal toxicity with severe magnesium wasting. Cidofovir has been used in renal transplant recipients; however, it often induces nephrotoxicity. Both foscarnet and cidofovir may exhibit synergistic nephrotoxicity with calcineurin inhibitors(28). One of the biggest challenges regarding anti-CMV treatment is the emergence of antiviral resistance. Although this is more commonly noted in lung and pancreas transplant recipients, CMV resistance to ganciclovir has also been observed in renal transplant recipients. Ganciclovir resistance should be suspected when patients have persistent, unchanged viremia and/or symptoms at 2 weeks into therapy, and in such cases, genotypic assays for the detection of mutations associated with antiviral resistance should be performed. Treatment of resistant isolates may include the use of foscarnet with or without ganciclovir, or cidofovir(29). Small case studies have demonstrated some efficacy of leflunomide for treating CMV disease in renal transplant patients. In a prospective study of 17 CMV-infected patients treated with leflunomide, 15 (88%) showed viral clearance and healing of infected organs(27). Other potential therapeutic agents for multidrug-resistant CMV include immunoglobulins, leflunomide, and artesunate, although data supporting their use remain anecdotal(30-32). Hence, there is a need to identify novel agents and strategies for the management of CMV infection and disease.

2. BK virus

BK virus, a human polyomavirus, is a small DNA virus belonging to the human papovavirus family. The incidence of BK virus infection after organ transplantation is approximately 2.5%, with onset usually within 1 year after transplantation(33-35). The kidney is the main site of latency. All immunosuppressive agents can induce BK virus

reactivation. Clinical complications of BK virus infection include hemorrhagic cystitis, ureteral stenosis, and interstitial nephritis; these complications may lead to graft failure(36). Reduction/adjustment of immunosuppression remains the cornerstone in the treatment or prevention of BK nephropathy(37-40). Because the reconstitution of the immune system in the control of infection takes 4 to 12 weeks, it is imperative to start treatment as early as possible(41). The one risk encountered with immunosuppression reduction is the development of acute rejection. The preliminary results of Wali et al.(42) reflect the protocol used at the University of Maryland, which consists of intensive screening with subsequent stepwise decrease in immunosuppression. This protocol has resulted in clearance of viremia with no graft loss or significant rejection diagnosed. Specifically, immunosuppression reduction is as follows: step 1, 50% decrease in the mycophenolate mofetil (MMF) dose immediately after diagnosis; step 2, 50% decrease in the target trough level of tacrolimus at 3 months if decoy cells persist; and step 3, elimination of MMF at 6 months if decoy cells persist. Maintenance dual therapy consists of the modified dose of tacrolimus and maintenance dose of prednisone (not exceeding 7.5~15 mg/week). In addition to decrease in immunosuppression, several centers have reported the use of several antipolyomaviral agents with anti-BK viral activity in vitro. These include cidofovir, leflunomide, quinolones, and intravenous immunoglobulin(37,40,43).

FUNGAL INFECTION

1. *Candida* species

The incidence of candidal infection ranges from 5% to 50% in transplant recipients, depending on the type of organ transplant(44). Pancreas and liver transplant recipients withRoux-en-Y anastomosis have risk factors for candidal infection. Use of muromonab-CD3 monoclonal antibody and immunomodulatory viral infections including CMV and HHV-6 are also factors that increase the risk of invasive fungal infection(45).

Universal fluconazole prophylaxis remains a controversial strategy in the prevention of invasive fungal infection. Randomized trial demonstrated deduction in candidal colonization and superficial infection, but compared with oral nystatin, no difference in the incidence of invasive infections was found(46). Fluconazole prophylaxis is recommended only in high-risk patients, whereas oral nystatin or clotrimazole may be considered in low-risk patients(45).

Amphotericin B remains the drug of choice for candidal infections (0.5~0.7 mg/kg per day). However, to avoid nephrotoxicity,less nephrotoxic lipid formulations may be considered in patients who can not tolerate conventional agents or in transplant recipients receiving calcineurin inhibitors. In addition, fluconazole use may be a reasonable treatment alternative for *Candida albicans* infection(47). Although *C. albicansis* the most common *Candida* species andissusceptible to fluconazole, the incidence of infections caused by other *Candida* species resistant to fluconazole is rising rapidly(48).

Caspofungin, the first echinocandin, has demonstrated activity against various *Candida* species(49). The combined use of cyclosporine and caspofungin may increase the overall exposure to caspofungin, thus increasing the risk of hepatotoxicity. On the other hand, early observations suggested that the concomitant use of caspofungin with tacrolimus led to decreased tacrolimus concentrations(49). Therefore, careful drug level monitoring is necessary.

2. *Aspergillus* species

Invasive aspergillosis is most commonly reported in lung and heart-lung transplant recipients and mostly occurs within 6 months after transplantation(45).

Amphotericin B is considered the first-line treatment for aspergillosis, but it may cause nephrotoxicity, particularly when the patient is receiving calcineurin inhibitors. Lipid formulations of amphotericin B are less likely to cause nephrotoxicity and can serve as substitutes, especially when chronic treatment is required for invasive aspergillosis(50).

Itraconazole shows activity against *Aspergillus* species, but itraconazole mono therapy is associated with higher relapse rates than amphotericin Bmonotherapy. However, itraconazole can be used as step-down oral therapy(51). Voriconazole and caspofungin show activity against invasive aspergillosis and may be used to avoid amphotericin B nephrotoxicity(51). Coadministration of voriconazole and sirolimus is contraindicated and close monitoring of cyclosporine and tacrolimus levels is warranted when these azole-calci-

neurin inhibitor combinations are used(52).

3. *Pneumocystis carinii*

Pneumocystis carinii pneumonia (PCP) is a common opportunistic infection in immunocompromised patients, including human immunodeficiency virus patients and transplant recipients. Although PCP prophylaxis is a routine practice, the drug regimen and therapy duration vary depending on the transplant center and type of organ transplanted(53). Trimethoprim-sulfamethoxazole provides excellent prophylaxis against PCP. Pentamidine (300 mg inhalation monthly) or dapsone (50~100 mg orally once daily) may also be used.

OTHER INFECTIONS

1. Toxoplasmosis

Toxoplasma gondii infection is of the greatest concern among heart transplant patients, but infection can occur in other types of transplant recipients, including kidney and liver recipients(54,55). *Toxoplasma* organisms can remain encysted within muscle tissue, such as cardiac muscle. Thus, infection is acquired as a result of the reactivation of cysts that remain dormant in the donor hearts of toxoplasma-seronegative children. Clinical manifestations can occur as early as 2 weeks after transplantation. Manifestations include pneumonia, fever syndrome, myocarditis, chorioretinitis, and central nervous system disease. Current prophylaxis includes pyrimethamine/sulfadiazine for donor (+)/recipient (-)patients. Trimethoprim-sulfamethoxazole is typically used in Recipient (+) patients. However, some experts also recommend trimethoprim-sulfamethoxazole for donor (+)/recipient (-)patients. The duration of prophylaxis is usually 6 months.

CONCLUSION

The epidemiology of infections after solid organ transplantation has shifted as a result of changes in immunosuppressive strategies and improved survival. Immunosuppression must be linked with appropriate vaccinations, donor and recipient screening, patient education regarding infectious risks and lifestyle, monitoring, and antimicrobial prophylaxis. The risk of infections has increased with the use of lymphocyte-depleting agents. Some drugs that alter the mobilization of lymphocytes (e.g., FTY720, a high-affinity agonist of sphingosine 1-phosphate receptor-1) or other components of the inflammatory response may alter the histology of infection and further confound diagnosis. Thus, it should be anticipated that with the introduction of each new immunosuppressive agent, there could be unique effects on the presentation and epidemiology of infection in organ transplant recipients.

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