REVIEW

ROBIN K. AVERY, MD
Department of Infectious Disease, Cleveland Clinic.

Infectious disease and transplantation: Messages for the generalist

ABSTRACT

Today, more patients than ever are receiving organ or bone marrow transplants and are surviving longer afterward. Because these patients often live far from the transplant center, their local primary care physicians may be called on to evaluate problems as they arise, although all significant issues should be handled in conjunction with the transplant team. This paper reviews the primary care physician's role in the pretransplantation evaluation, and in coordination of long-term care, as well as illustrative cases.

KEY POINTS

Primary care physicians can reinforce educational points, such as how to avoid infections from food and other environmental exposures.

The primary care physician should review the transplant candidate's vaccination status on an ongoing basis and give the longer-acting vaccines before end-stage organ dysfunction would render them less effective.

Opportunistic infections are most often seen 1 to 6 months after transplantation. During this period, cytomegalovirus (CMV) often directly causes infectious syndromes and indirectly makes the patient more susceptible to opportunistic infections.

INCREASING NUMBERS of patients are receiving organ or bone marrow transplants, and thanks to modern immunosuppressive and prophylactic antimicrobial regimens, more of them are surviving well past the early posttransplantation period. Since more and more patients are receiving transplants at centers far from where they live, the local primary care physician or medical subspecialist often must initially evaluate problems that arise, particularly late after transplantation.

In determining if a situation needs urgent evaluation by the transplant team, primary care physicians should have some understanding of the principles of transplantation-related infectious disease. However, since even a seemingly minor problem may be an early sign of a major infectious complication, they also need frequent, ongoing communication with the transplant team—including clinicians with special training in transplantation-related infectious disease. In addition, since many medications can interact with the immunosuppressive drugs (mainly cyclosporine and tacrolimus) that transplant recipients receive, the transplant team needs to be kept informed of all medication changes.

This case-based review follows the general timetable of infection after solid organ and bone marrow transplantation. The focus is on how to manage clinical problems that arise long after transplantation and, therefore, outside the transplantation center. Other issues covered include:

- Pretransplantation evaluation.
- Rationale for an ongoing prophylactic regimen.
- Fever in a transplant recipient.
- Drug interactions.

- Common questions and concerns about transplantation.
- Educating transplant recipients about infection risks.

THE PRETRANSPLANTATION EVALUATION

Before transplantation, patients undergo an evaluation to detect past or present infections that require treatment, and to define the risk of certain infections and the required prophylactic regimen (TABLE 1).[1]

Standard serologic screening

In addition to a careful history and physical examination, most centers use a battery of serologic screening tests. The tests included are largely standardized but may vary from one center or organ program to another; the tests detect exposure to:

- Cytomegalovirus (CMV).
- Epstein-Barr virus.
- Hepatitis B and C viruses.
- Herpes simplex virus.
- Varicella-zoster virus.
- Human immunodeficiency virus (HIV).
- Human T-cell leukemia virus I (HTLV-I).
- Syphilis (by rapid plasma reagin testing).

A seemingly minor problem may signal a major infection

The results of these tests have important implications. Tests may reveal that transplantation is inadvisable, as in a potential recipient previously unaware of being HIV-seropositive. Or they may reveal a condition such as chronic active hepatitis C virus infection, which requires further evaluation before transplantation can be considered.

These tests also influence the choice of prophylactic medications given after transplantation, according to the center's protocols. For example, a CMV-seronegative recipient who receives an organ from a CMV-seropositive donor is at high risk for developing symptomatic primary CMV infection, and should receive aggressive prophylactic treatment for CMV.[1]

Further tests

Tuberculosis. All patients, especially international ones, should undergo tuberculin skin testing with purified protein derivative (PPD), and also with a panel of *Candida*, *Trichophyton*, and tetanus controls. The latter are necessary because preexisting disease or medications or both may render the patient anergic and therefore can cause the tuberculin skin test to be misinterpreted as negative.

Toxoplasma gondii. Serologic testing for *Toxoplasma gondii* is useful, particularly in potential heart recipients, because this parasite can persist in myocytes and may be transmitted through heart transplantation. The highest risk for transmission is from a *Toxoplasma*-seropositive heart donor to a seronegative recipient, and some transplantation programs give these patients pyrimethamine prophylactically.

Histoplasmosis, coccidioidomycosis. Serologic testing is indicated for patients who have lived in areas where these mycoses are endemic.

Strongyloides. International patients or those otherwise at risk should have three stools tested for *Strongyloides* (ova and parasite examinations are preferred), and serologic testing for *Strongyloides* should be considered (with or without the addition of empiric thiabendazole therapy, given the high mortality of disseminated strongyloidiasis).

Vaccinations

A vaccination history is important,[2] since vaccines are often more effective before transplantation than afterward. Every effort should be made by both the transplant team and the primary care physician to give any that are indicated, including pneumococcal polysaccharide vaccine, tetanus-diphtheria toxoid vaccine, hepatitis B vaccine, and varicella vaccine for seronegative patients. These may also have suboptimal effects *before* transplantation, because transplant candidates often have organ dysfunction and metabolic abnormalities; nevertheless, it is useful to vaccinate patients before they begin receiving immunosuppressive therapy.

Tetanus. Given anecdotal reports of cases in which tetanus-diphtheria toxoid vaccine was thought to have precipitated transplant rejection, and given the reluctance of some physicians to give it after transplantation, it would seem advisable to update the tetanus-diphtheria toxoid vaccine booster before transplantation.

Chickenpox. Primary varicella can be

devastating in immunocompromised patients, and prophylactic therapy with varicella-zoster immune globulin after exposure is not always completely effective[3]; therefore, varicella vaccine should be considered in potential recipients who are seronegative. Of note: because some patients who do not recall having chickenpox may actually be seropositive, serologic testing beforehand is important.

Donor screening

Potential donors also undergo a battery of serologic tests. Donors testing positive for HIV or hepatitis B surface antigen are excluded; those testing positive for CMV or other infections may be accepted, but the transplant recipients may need prophylactic therapy. Donors who are hepatitis B surface antigen-negative but core antibody-positive are often used, except for liver transplantation. The risk to non-liver recipients appears to be low, but is not zero, which is another reason why potential recipients should receive hepatitis B vaccination.

Primary care before transplantation

Although testing and vaccination protocols may be part of the transplantation center's practice, it is always wise for the primary care physician to review the transplantation candidate's vaccination status on an ongoing basis, and to try to give the longer-acting vaccines before end-stage organ dysfunction would render them less effective.

The primary physician or specialist referring the patient for transplantation can also prevent morbidity and delays by evaluating carefully for past or current infection, and by highlighting details of any infectious episodes in the information provided to the transplantation center.

THE TIMETABLE OF INFECTION AFTER SOLID-ORGAN TRANSPLANTATION

The infections seen after solid-organ transplantation, in general, follow a classic timetable, as outlined by Rubin.[1] The scenario described in CASE 1 is not typical, but it illustrates the variety of infections that can occur at different periods after transplantation and the timetable they appear to follow.

TABLE 1

Screening tests and vaccinations before transplantation

SCREENING TESTS TO CONSIDER FOR ORGAN AND BONE MARROW RECIPIENTS
Cytomegalovirus (CMV) IgG, IgM
Hepatitis B virus (HBV) Hepatitis B surface antigen, HBcIgM and IgG hepatitis B surface antibody (HBV-DNA where appropriate)
Hepatitis C virus (HCV) Serologic testing (HCV-RNA where appropriate)
Herpes simplex virus (HSV) IgG (if prophylactic protocols depend on serologic testing)
Human immunodeficiency virus (HIV) Enzyme-linked immunoadsorbent assay (ELISA) Western blot for seropositive patients
Human T-cell leukemia virus I (HTLV-I) ELISA; Western blot for seropositive patients
Syphilis Rapid plasma reagin
Toxoplasma IgM and IgG, particularly in potential heart recipients
Tuberculosis Purified protein derivative and anergy panel
Varicella-zoster virus (VZV) IgG
SCREENING FOR SELECTED PATIENTS AT RISK
Coccidioidomycosis, histoplasmosis Serologic testing
Strongyloides Testing of three stool samples; serologic testing; consider empiric thiabendazole therapy
VACCINATIONS
Pneumococcal polysaccharide vaccine (if not given within 6 years)
Influenza vaccine (yearly)
Hepatitis B series (0, 1, and 6 months)
Varicella vaccine (for seronegative patients)
Tetanus/diphtheria toxoid (if needed)
Polio booster if needed (use inactivated injection, not live oral vaccine if taking immunosuppressive medications)
Measles-mumps-rubella, if needed (not for patients taking immunosuppressive medications)

The first month

In the first month after transplantation, doses of immunosuppressive medication are at their highest, but the immune system has not yet felt their effects, and the infections seen are primarily surgical, including those related to the wound, intravenous line, urine, and lungs.

Occasionally, a partially treated or untreated infection in the donor or the recipient can manifest itself during this period. Untreated bacteremia in the donor should lead to aggressive treatment after transplantation in the recipient.

A recent category of posttransplantation infections includes preexisting infections related to the long-term use of left ventricular assist devices prior to heart transplantation.

From 1 to 6 months

In the second period—from 1 to 6 months after transplantation—opportunistic infections are most often seen.

Cytomegalovirus (CMV) infection can cause or contribute to several problems during this period:

- Direct infectious syndromes (fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, gastrointestinal tract disease).
- Increased immunosuppression and susceptibility to opportunistic infections such as fungal infections and *Pneumocystis carinii* pneumonia.[1,6]
- A possible role in allograft dysfunction, such as allograft vasculopathy in heart recipients and bronchiolitis obliterans in lung recipients.
- Epstein-Barr virus-related posttransplantation lymphoproliferative disease.[7]

Vaccines are often more effective before transplantation than after

CMV prophylactic protocols vary widely and depend on the patient's level of risk. Patel et al[8] recently reviewed the vast literature on CMV prophylaxis. Serologic status is a key factor, with CMV-negative recipients of CMV-positive grafts (D+/R-) being at highest risk for symptomatic infection. Recipients who are CMV-positive before transplantation can also develop CMV syndromes by reactivation of latent virus or by superinfection in cases where the donor is also CMV-positive. CMV-negative recipients of CMV-negative grafts (D-/R-) are at relatively low risk as long as they receive CMV-free blood products. Augmented immunosuppression, particularly with the antilymphocyte therapies muromonab-CD3 and antithymocyte globulin, increases the CMV risk significantly in seropositive recipients, but this can be counteracted by concomitant ganciclovir administration.[9]

Other opportunistic pathogens seen during this period include *Pneumocystis*, herpes simplex virus, varicella-zoster virus, *Listeria*, *Nocardia*, *Toxoplasma*, Epstein-Barr virus, *Candida*, *Cryptococcus*, and *Aspergillus*.[1] Many of these infections are easier to prevent than to treat when full-blown. Hence, prophylactic therapy is important during this period. As noted above, patients who cannot tolerate trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis carinii* pneumonia may be at higher risk for *Listeria*, *Nocardia*, and *Toxoplasma* infections. If trimethoprim-sulfamethoxazole therapy has been stopped for any reason other than a severe allergic reaction, it may be worthwhile to consider a careful rechallenge (TABLE 2).

After 6 months

After 6 months, transplant recipients fall into three groups.[1]

- Patients who receive minimal maintenance immunosuppressive therapy and who have no significant impairment of transplant organ function are unlikely to have opportunistic infections, although occasionally pathogens such as *Legionella* may be seen. Influenza and pneumococcal vaccine should be given. Screening for cancer of the skin, cervix, breast, colon, and prostate is important, as these patients are at increased risk for malignancy.
- Patients who have had considerable ongoing problems with rejection and have required augmented immunosuppression are at risk for all the opportunistic infections seen in the second posttransplantation period. They are candidates for continued prophylactic treatment even if the transplant center's protocol does not usually require it. These patients require particular attention and frequently benefit from the involvement of a transplant infectious disease physician.
- Patients who have done well in terms of allograft function but who then experience progressive chronic infection with immunomodulating viruses (hepatitis B and C virus, and CMV in the form of retinitis.)

EVALUATING THE FEBRILE PATIENT AFTER SOLID-ORGAN TRANSPLANTATION

If a recipient of a solid-organ transplant develops a fever, the physician should consider the time period after transplantation and the

CASE 1

Complications in an organ transplant recipient

A 45-year-old woman underwent orthotopic liver transplantation in May 1995 for cryptogenic cirrhosis.[4] The donor was CMV-seropositive and the recipient CMV-seronegative (D+/R-). She experienced severe early rejection and required high-dose steroids, muromonab-anti-CD3 (OKT3), and plasmapheresis, in addition to cyclosporine and azathioprine.

Despite prophylaxis with 2 weeks of intravenous ganciclovir and intermittent CMV hyperimmune globulin,[5] she developed several episodes of relapsing CMV hepatitis requiring ganciclovir, and a Hickman catheter was placed because of poor venous access. Seven months after transplantation, a liver biopsy showed fatty changes indicative of toxic hepatopathy; ganciclovir therapy was discontinued, and trimethoprim-sulfamethoxazole therapy was replaced by aerosolized pentamidine as prophylaxis against *Pneumocystis carinii* pneumonia.

Several months later, with the Hickman catheter still in place, the patient developed low-grade fevers, chills, and malaise without localizing symptoms, except for some intermittent sinus drainage. Serum liver enzyme levels were moderately elevated, as they had been for several months.

The patient's physician obtained sinus films and a chest radiograph, which were normal. The fevers appeared to subside, and she was told she had a viral illness. Later, however, she was diagnosed with *Listeria monocytogenes*-related right-sided endocarditis, and she developed septic pulmonary emboli and arrhythmias. At nearly 2 years after this episode, the patient is clinically well without evidence of infection, though there is evidence of chronic rejection.

THE IMMUNOSUPPRESSED PATIENT: LESSONS LEARNED

This case illustrates the fragile condition of the very immunosuppressed transplant recipient. This patient is at very high risk for rejection and susceptibility to opportunistic infections. Her high-risk (D+/R-) CMV status likely contributed to the complexity of her course.

Fortunately, not all transplant patients are this ill. Many who have done well with their allografts and who are on minimal immunosuppressive regimens are mostly subject to the same infections as healthy persons: eg, influenza, urinary tract infection, and pneumococcal pneumonia.[1] However, this case underscores the point that the presenting manifestations of a life-threatening infection in some transplant recipients may be rather subtle. The urgency of the evaluation must take into account what Rubin[1] has termed the "net state of immunosuppression" of the patient. It is best to contact the transplant center for advice and further evaluation.

This case also illustrates several other important points.

Foreign body raises risk. First, the presence of a foreign body such as a Hickman or Foley catheter, or any other breach in the normal mucosal barriers, represents an increased risk for infection in these patients. The need for such a device should be carefully evaluated and reevaluated regularly.

CMV raises risk. Second, a patient with CMV, particularly tissue-invasive or recurrent CMV, is at increased risk for fungal or other opportunistic infections[1,6] due to the additional immunosuppression conveyed by CMV infection itself.

Trimethoprim-sulfamethoxazole important. Finally, the importance of trimethoprim-sulfamethoxazole cannot be overemphasized. In addition to being the most effective prophylaxis for *Pneumocystis*, it also likely confers at least some protection against other infectious agents, including *Listeria*, *Nocardia*, and *Toxoplasma*, as well as common urinary tract and some upper respiratory pathogens.

group to which the patient belongs in the above schema. This can help to focus the evaluation and the decision as to how urgently the patient needs to return to the transplant center, in the case of a patient who lives far from the transplant center.

The following is a list of important questions and considerations in the evaluation.

History

- What is the time period after transplantation?
- What is the degree of impairment of the transplanted organ? How many episodes of rejection have there been? How severe? What is the current steroid dose? Was muromonab-CD3 or antithymocyte globulin given?
- What is the patient's CMV serostatus? Is there a history of CMV viremia or symptomatic CMV?
- Has the patient been exposed to such risks as hospital construction, ill contacts, questionable food (*Listeria*, *Salmonella*, *E coli*

TABLE 2

Prophylactic measures for the early posttransplant period

TYPE OF INFECTION	PROPHYLAXIS
Herpes simplex virus, varicella-zoster virus	Acyclovir, for patients not receiving ganciclovir
Cytomegalovirus	Varies*; regimens involving ganciclovir, acyclovir, cytomegalovirus immune globulin, intravenous immune globulin, or combinations
***Pneumocystis carinii* pneumonia**	Trimethoprim-sulfamethoxazole if possible, aerosolized pentamidine if not
Fungal infections	Mucosal yeast prophylaxis with clotrimazole or nystatin; azoles in selected patients
Bacterial infections	Trimethoprim-sulfamethoxazole when possible; substitute ciprofloxacin in allergic kidney recipients
Hepatitis B virus†	Hepatitis B immune globulin, newer antiviral agents under evaluation

*See Patel et al, reference 8; †For liver transplant recipients at risk for recurrence of hepatitis B virus infection

O157:H7, hepatitis A), or travel? Was the patient exposed to tuberculosis or *Strongyloides* before transplantation?

- What prophylaxis is being given for *Pneumocystis carinii* pneumonia (trimethoprim-sulfamethoxazole or another agent)?

Prophylaxis for CMV depends on risk level and serologic status

Physical examination

A thorough physical examination is important, with particular attention to the sinuses, pharynx, nodes, chest, heart, abdomen, liver and spleen, and skin. Are there any masses? Also check incisions, drains, and indwelling catheters, and examine for lymphoceles and rashes.

Chest radiography

Is there a diffuse pattern (typical of CMV, *Pneumocystis carinii* pneumonia, respiratory virus infection)? Are there nodules (*Aspergillus*, *Nocardia*, *Rhodococcus*), cavities (fungi, mycobacteria), focal infiltrates? Is there evidence of adenopathy (posttransplantation lymphoproliferative disease, acid-fast bacillus infection, histoplasmosis)?

Note that computed tomography (CT) of the chest may provide much more information (eg, about occult fungal nodules) than the plain chest radiograph. Consider early bronchoscopy and full infectious disease evaluation of bronchoscopic lavage fluid and transbronchial biopsy specimens in patients with unexplained dyspnea or hypoxemia, with or without findings on chest radiography.

Additional imaging tests

Abdominal CT (abscess, adenopathy), sinus films, and head CT (toxoplasmosis, aspergillosis, *Nocardia*) may be indicated. Ultrasonography of the renal allograft may identify obstruction or fluid collections such as infected lymphoceles.

Ultrasonography of the right-upper quadrant will visualize the liver and biliary system and can also demonstrate the patency of vessels in liver transplant recipients. It can also indicate veno-occlusive disease in bone marrow transplant recipients.

Cultures

These are dictated by the clinical situation, but consider testing the blood, urine, and sputum for bacterial and fungal pathogens. Blood samples for CMV detection may be processed by the buffy coat (shell-vial and tissue culture), polymerase chain reaction, antigenemia assay, hybrid-capture DNA assay, or other modality. Occasionally consider examination of the stool (ova and parasites, enteral bacterial pathogens, and *Clostridium difficile*), the

cerebrospinal fluid, drainage tubes, skin lesions, and other sites.

Blood work

Rule out allograft dysfunction; leukopenia due to CMV, ganciclovir, or azathioprine; elevated liver enzyme levels due to CMV, rejection, hepatitis A virus, hepatitis B virus, hepatitis C virus, or medications; and hypogammaglobulinemia (especially in bone marrow or late solid-organ recipients).

Consider disseminated histoplasmosis, coccidioidomycosis, and nontuberculous mycobacteria (fungal serology panel; fungal and acid-fast bacillus isolator blood cultures), particularly in patients with pancytopenia and systemic symptoms, with or without a localizing focus.

Endoscopy, colonoscopy, small bowel radiography

Rule out gastrointestinal CMV, Epstein-Barr virus-related posttransplantation lymphoproliferative disease (lymphoma), C *difficile*, and *Helicobacter pylori*, and also graft-vs-host disease in allogeneic bone marrow transplant recipients.

DRUG INTERACTIONS AFTER SOLID-ORGAN TRANSPLANTATION

For any clinician treating transplant recipients, a knowledge of medication interactions is crucial. The list of medications that affect levels of cyclosporine and FK-506 (tacrolimus) is immense, but awareness of the most common interactions may prevent an untoward event. For example, a sudden fall in the cyclosporine level may precipitate acute rejection, whereas an unintended rise in the cyclosporine level can lead to renal dysfunction or other toxicity (TABLE 3).

It is important to be aware of these interactions when starting, for example, an antibiotic for bronchitis or sinusitis. One approach is to anticipate the problem, decreasing the cyclosporine dose and following the levels closely, with the advice and consent of the transplant center. Before using any new medication in a transplant recipient, it is always a good idea to research possible drug interactions, speak to a transplant specialist, or both.

TABLE 3

Drug interactions: cyclosporine and antibiotics

RAISE CYCLOSPORINE LEVELS	PRODUCE SYNERGISTIC NEPHROTOXICITY WITH CYCLOSPORINE
Azithromycin	Aminoglycosides
Clarithromycin	Amphotericin
Erythromycin	Foscarnet
Fluconazole	Pentamidine
Itraconazole	Quinolones (high doses, occasionally)
Ketoconazole	Trimethoprim-sulfamethoxazole (high doses; occasionally)
LOWER CYCLOSPORINE LEVELS	
Isoniazid	
Rifampin	

SOURCE: ADAPTED FROM RUBIN, REFERENCE 1.

An exhaustive list of the interactions of drugs other than anti-infectives is not possible in this article. Nevertheless, be aware of possible harmful interactions of transplant-related drugs other than cyclosporine, such as the interaction of azathioprine and allopurinol leading to potentially serious leukopenia. In all cases, medication changes should be discussed with the transplant center.

The presence of catheters increases the risk of infection

INFECTION TIMETABLE AFTER BONE MARROW TRANSPLANTATION

A wide variety of infections can occur at any time following allogeneic bone marrow transplantation, even several years after, as seen in CASE 2. As in solid-organ transplantation, there are three periods with respect to risk for infection.

The first 3 weeks

The first time period is that of neutropenia, lasting an average of 3 weeks after receiving donor marrow or stem cells. During this time, as in other febrile neutropenic patients, the principal threats are from bacteria and fungi. Standard prophylaxis includes combination antimicrobial therapy for fever; an antifungal such as amphotericin B in low doses (at some centers), with an increase in the dose if fever persists; acy-

CASE 2

Bone marrow transplant complications

A 45-year-old man underwent allogeneic bone marrow transplantation 4 years ago for acute lymphocytic leukemia. Chronic graft-vs-host disease of the lung (bronchiolitis obliterans) required continuation of steroids over a long period of time. Despite various prophylactic antibiotic regimens, he developed multiple episodes of recurrent infection, including pneumonia, bronchitis, sinusitis, and culture-negative sepsis. Ultimately he was found to be profoundly hypogammaglobulinemic. Intravenous immune globulin was reinstituted and his infectious episodes diminished.

clovir for herpes simplex virus and varicella-zoster virus prophylaxis; and trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia prophylaxis.

Early after engraftment

The second time period is the early postengraftment period, or approximately the first year after transplantation, though this depends on the patient. Although the white blood cell count has returned to normal, the immune system is far from being completely reconstituted. Immunoglobulin class and subclass deficiencies, and abnormalities of T cells and other cellular immune functions may persist for a long time. Intravenous immune globulin is frequently given, weekly at first and then less frequently, to diminish the frequency and severity of graft-vs-host disease, CMV infection, and bacterial infections. As CASE 2 shows, some patients may require intravenous immune globulin even years after transplantation.

Avoid live virus vaccines in transplant recipients

Graft-vs-host disease is itself an immunosuppressing condition, and it is treated with immunosuppressive medications, so patients with graft-vs-host disease are at increased risk for all types of infection.

Prophylaxis during this period is directed at CMV, *Pneumocystis carinii*, bacterial, and fungal infection. One option for CMV prophylaxis is ganciclovir, given through the 100th day after transplantation.[10,11] CMV in bone-marrow transplant patients can be extremely severe, especially if pneumonitis develops. It is therefore important to institute effective CMV prophylaxis and close monitoring. After ganciclovir is discontinued, acyclovir is substituted as herpes simplex virus and varicella-zoster virus can be major problems.

At our center, antifungal drugs (currently itraconazole[12]) are given as long as patients remain on immunosuppression, but invasive aspergillosis remains a significant problem, especially in patients with severe graft-vs-host disease. Trimethoprim-sulfamethoxazole serves as prophylaxis against *Pneumocystis carinii* pneumonia and other bacterial infections. In patients who cannot tolerate trimethoprim-sulfamethoxazole, alternatives include aerosolized pentamidine plus an antibiotic that covers pneumococci. Patients with graft-vs-host disease of the gastrointestinal tract tend to have protracted courses and profound immunosuppression; the disruption of gut mucosa makes them vulnerable to gram negative bacteremias and intra-abdominal abscesses, and prophylaxis directed at abdominal organisms is included.

Late after engraftment

The third, or late, posttransplantation period may be marked by quiescence or punctuated with recurrent infections. Encapsulated organisms such as pneumococci are seen most frequently. Chronic graft-vs-host disease may alter skin, oropharynx, and sinus mucosa, creating more portals for infection. Hypogammaglobulinemia may occur. Prophylaxis in this period is individualized, depending on the degree of immunosuppression, the presence and location of graft-vs-host disease, and the degree to which the immune system has successfully reconstituted itself.

COMMON ISSUES FOR ORGAN AND BONE MARROW TRANSPLANTATION

Chickenpox exposure

For solid-organ recipients, preexisting immunity generally persists. If the physician is concerned or if the varicella-zoster virus serostatus is negative or unknown, varicella-zoster immune globulin, acyclovir, or both may be given prophylactically; however, varicella-

zoster immune globulin may not be completely effective.[3] Exposure to herpes zoster may also result in primary varicella for the susceptible patient and should prompt prophylaxis, though herpes zoster is less contagious than varicella.

Vaccinations for patients and close contacts

If possible, hepatitis B vaccine, pneumococcal vaccine, and varicella vaccine should be given before transplantation, when response is likely to be highest. Avoid live vaccines (oral polio, measles-mumps-rubella) in transplant recipients. Household members should receive inactivated rather than oral polio vaccine. Transplant recipients should receive pneumococcal polysaccharide vaccine and influenza vaccine even though response may be suboptimal. Many clinicians repeat the pneumococcal vaccine every 2 to 3 years.

Revaccination after bone marrow transplantation

Protocols for revaccination after bone marrow transplantation vary from center to center.

CMV transmission to others

The patient with active CMV infection would be prudent to stay away from pregnant women whose serostatus is unknown, or other immunocompromised individuals.

INFECTION PREVENTION: FOOD AND EXPOSURE COUNSELING

Transplant patients need not wear space suits or live in bubbles, and indeed it is important for quality of life that they be able to maintain many normal activities.

However, it is prudent to advise them on simple matters that may prevent serious infection. Specific guidelines may be provided by the transplant center or hospital infection control committee.

Any meat and eggs consumed should be well cooked. Patients should be counseled to avoid fast food (exposure to *E coli* O157:H7, *Salmonella*) and soft cheeses (*Listeria*). Any leftovers should be well heated (eg, *Listeria* from turkey franks).

To avoid exposure to *Aspergillus*, exposure to construction, dust, soil, fertilizer, compost heaps, and decaying matter should be minimized. If such contact is inevitable, effective masks should be worn and changed frequently. It is advisable for inpatients to wear masks when traveling off the hospital floor, but especially those who have undergone organ transplantation or who are particularly immunosuppressed.

The importance of hand washing (by patients, family members, and healthcare workers) cannot be overemphasized.

Overseas travel should be carefully thought out and medical advice sought well in advance.

Exposure to tuberculosis should be avoided (eg, working in a shelter for the homeless would not be a good choice of occupation).

The patient without a definite recollection of varicella infection should have a titer checked to determine risk if an exposure should occur.

Blood products should be CMV-free for CMV-seronegative patients. Some clinicians feel this should be the case for all transplant recipients.

Any fever or chills, or any illness more than a mild upper respiratory infection should be reported immediately so that evaluation can proceed rapidly.

Tell transplant recipients how to reduce infection risk from food and the environment

SUMMARY

Fortunately, most of the time, patients who are stable long after transplantation present with uncomplicated upper respiratory or urinary tract infections rather than esoteric pathogens. Even in these cases, however, prompt treatment and evaluation are important. For example, urinary tract infections are more likely to be associated with bacteremia in these patients.

The primary care physician plays a crucial role in differentiating these episodes from those requiring more serious and lengthy evaluation. A constant flow of communication with the transplant center is essential, and particularly for patients with complex problems, the involvement of an infectious disease specialist with specific training in transplant infectious disease is frequently helpful.

REFERENCES

1. **Rubin RH.** Infection in the organ transplant recipient. In Rubin RH, Young LS, editors. Clinical Approach to Infection in the Compromised Host. 3rd ed. New York: Plenum Medical Book Company, 1994:629–705.
2. **Hibberd PL, Rubin RH.** Approach to immunization in the immunosuppressed host. Infect Dis Clin North Am 1990; 4:123–142.
3. **Lynfield R, Herrin JT, Rubin RH.** Varicella in pediatric renal transplant recipients. Pediatrics 1992; 90:216–220.
4. **Avery RK, Barnes D, Teran JC, et al.** *Listeria monocytogenes* tricuspid valve endocarditis with septic pulmonary emboli in a liver transplant recipient. Personal communication, 1998.
5. **Falagas M, Snydman DR.** Evaluation of a liquid and virally inactivated formulation of cytomegalovirus immune globulin combined with ganciclovir in liver transplant recipients at risk for primary infection. Personal communication, 1998.
6. **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.
7. **Basgoz N, Hibberd PL, Tolkoff-Rubin NE, et al.** Possible role of cytomegalovirus disease in the pathogenesis of post-transplant lymphoproliferative disorder. Abstract P-150, 12th Annual Meeting, American Society of Transplant Physicians, Houston, 1993.
8. **Patel R, Snydman DR, Rubin RH, et al.** Cytomegalovirus prophylaxis in solid organ transplant recipients. Transplantation 1996; 61:1279–1289.
9. **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; 123:18–26.
10. **Winston DJ, Ho WG, Bartoni K, et al.** Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Ann Intern Med 1993; 118:179-184.
11. **Goodrich JM, Bowden RA, Fisher L, et al.** Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 1993; 118:173–178.
12. **Avery R, Longworth D, Pohlman B, et al.** Prophylaxis of invasive aspergillosis with itraconazole in allogeneic bone marrow transplant recipients. Abstract #531, 16th Annual Meeting, American Society of Transplant Physicians, Chicago, 1997.

ADDRESS: *Robin K. Avery, MD, Department of Infectious Disease, S32, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195-5215, e-mail averyr@cesmtp.ccf.org.*