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CHAPTER 60

POSTTRANSPLANT INFECTIONS

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1. **What type of infections do kidney transplant recipients develop?**
   - Donor-derived infections
   - Recipient-derived infections
   - Nosocomial-acquired infections
   - Community-acquired infections

2. **Is there any pattern to infections that occur post transplantation?**
   Yes. Karuthu et al. reviewed this recently, including the timing of infections post transplant. Infections occur in a generally predictable pattern after kidney transplantation. See Fig. 60.1
   - First month post transplant:
     - Nosocomial and surgery-related infections are the predominant infections
     - Aspiration pneumonia
     - Catheter infections
     - Wound infections
     - Anastomotic leaks
     - Clostridium difficile colitis
     - Resistant organisms such as methicillin-resistant *Staphylococcus aureus*
   - Months post transplantation 1 through 6:
     - Activation of latent infections is most common
     - *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia
     - Fungal infections
     - Herpes-related disease
     - BK virus
     - *Clostridium difficile* colitis
     - Hepatitis C virus
     - Adenovirus
     - Influenza
     - C*ryptococcus*
     - *Mycobacterium tuberculosis*.
   - Posttransplant month 6 and beyond:
     - Community-acquired infections are predominant (urinary tract infections [UTIs], pneumonia)
     - Fungal infections, including Nocardia, Aspergillus, and Mucor
     - Late viral infections (cytomegalovirus [CMV], hepatitis B and C, herpes simplex virus, John Cunningham (JC) virus)

3. **What is the most common bacterial infection that leads to hospitalizations in kidney transplant patients?**
   UTIs. The most common bacterial cause is *Escherichia coli*.

4. **What infectious prophylaxis do patients receive post transplant?**
   - Valganciclovir to prevent CMV for 3 to 6 months
   - Trimethoprim-sulfamethoxazole to prevent *Pneumocystis jirovici* and UTIs for 6 months
   - Nystatin or clotrimazole to prevent esophageal candidiasis for 3 months

5. **What is BK virus?**
   BK virus is a ubiquitous, double-stranded DNA polyomavirus with a 5300–base pair genome that replicates in the host nucleus. The polyoma family includes JC virus (infectious cause of progressive multifocal leukoencephalopathy [PML]), SV40, and monkey polyomavirus. Although the human polyomaviruses are highly seroprevalent in humans, they appear to cause clinical disease only in immunocompromised hosts.

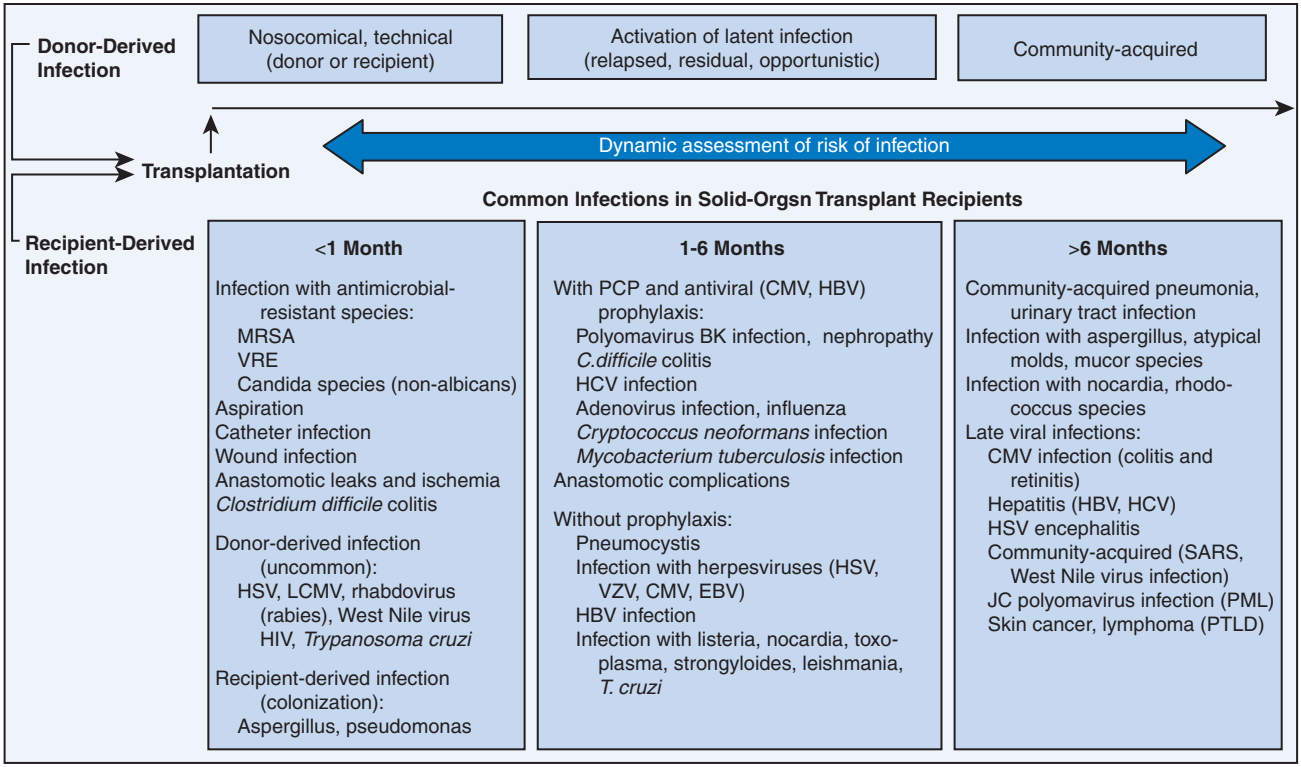

Figure 60.1. Timeline of common infections in transplant recipients. *CMV*, Cytomegalovirus; *EBV*, Epstein-Barr virus; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HSV*, herpes simplex virus; *LCMV*, lymphocytic choriomeningitis; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *PCP*, *Pneumocystis jiroveci* pneumonia; *PML*, progressive multifocal leukoencephalopathy; *PTLD*, posttransplant lymphoproliferative disorder; *SARS*, severe acute respiratory syndrome; *VRE*, vancomycin-resistant enterococci; *VZV*, varicella-zoster virus. (From *New England Journal of Medicine,* Fishman, J. A., *Infection in solid-organ transplant recipients,* Volume 357, page 2606, Copyright 2007 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

6. What is BK-associated nephropathy?

BK virus damages the transplant kidney. The prevalence of BK nephropathy ranges from 1% to 10%. BK nephropathy is characterized by a tubulointerstitial disease pattern that closely resembles acute rejection.

7. Besides nephropathy, can BK virus cause any other kidney problems?

Yes. BK virus is associated with ureteral stenosis/strictures, which may lead to obstructive uropathy. Obstructions associated with BK virus usually occurs 2 to 4 months post transplant, whereas ischemia-induced stenosis usually occurs 1 to 2 weeks postoperatively.

8. What are the risk factors for the development of BK-associated nephropathy?

- Human leukocyte antigen mismatch
- Previous acute rejection
- Use of lymphocyte depleting therapy
- Use of steroid pulses
- Age >55
- Male gender
- White race
- Diabetes

9. Discuss BK screening.

BK virus is detectable both in the blood and the urine. The virus first appears in the urine (viruria) and then is detectable in the blood (viremia) several weeks later. The preferred screening test at most transplant centers is the blood BK quantitative viral DNA polymerase chain reaction (PCR). The sensitivity between the serum and urine BK viral testing is the same at 100%, but the specificity of serum testing is 90% versus 80% for urine testing. BK viremia is also a better predictor of BK nephropathy. There is an alternative strategy that does use BK viruria for screening because it appears earlier that BK viremia. Once BK viruria is present, the clinician considers lowering immunosuppression and now switching to BK viremia for screening.

Recommended screening times are monthly for the first 6 months and then every 3 months up to 24 months post transplant.

A BK viral load greater than 10,000 copies is strongly associated with BK nephropathy. BK viruria greater than 1,000,000 copies is associated with BK nephropathy. The next step is a kidney transplant biopsy, which is the gold standard to confirm the diagnosis and see the degree of nephropathy.

10. What does the kidney biopsy show in BK-associated nephropathy?

Biopsy remains the gold standard for the diagnosis of BK-associated nephropathy. BK virus can induce a number of characteristic changes on kidney biopsy, including intranuclear viral inclusions, tubular injury/tubulitis, and tubulointerstitial inflammation. Because none of these kidney biopsy findings are pathognomonic for BK-associated nephropathy, the diagnosis must be confirmed by demonstrating antibodies against BK with immunohistochemistry.

11. What does urine cytology show in BK-associated nephropathy?

Cytologic examination of the urine can detect BK-infected cells ("decoy cells"). These characteristic cells have enlarged nuclei with a single, basophilic, intranuclear inclusion. Identification of decoy cells is sensitive, but not specific, for the diagnosis of BK-associated nephropathy.

12. What is the treatment for BK-associated nephropathy?

The goal in treating BK-associated nephropathy is to eradicate the virus while maintaining kidney function and preventing acute or chronic rejection. Most treatments of BK-associated nephropathy involve reducing immunosuppression to permit native, immune-mediated handling of the BK virus. Possible strategies include discontinuation of a single immunosuppressive agent, reduction of dosages, and steroid avoidance. Antiviral therapy with leflunomide or cidofovir has been used in conjunction with decreasing immunosuppressants in some instances. IVIG also has been used, particularly in patients with concomitant acute rejection.

13. Can patients with graft failure resulting from BK nephropathy be retransplanted?

Yes. Transplant nephrectomy is usually not indicated. Ideally the BK viral load should be undetectable in the serum by PCR at the time of transplant.

14. Discuss CMV, including risk factors for the development of CMV infections post transplantation.

CMV is a member of the genus *Herpesvirus* and belongs to the family *Herpesviridae*. It is composed of a double-stranded DNA genome. Exposure to the virus, as indicated by immunoglobulin G anti-CMV

antibodies, is present in more than two-thirds of donors and recipients prior to transplantation. CMV can be transmitted from the donor either by blood transfusions or by the transplanted kidney. Symptomatic CMV infection occurs in 20% to 60% of all transplant recipients and is a significant cause of morbidity and mortality.

Risk factors associated with the development of CMV infections post transplantation include lymphocyte-depleting induction therapy, high-dose MMF, and the absence of adequate antiviral prophylaxis.

15. What groups are at highest risk from CMV infections?

Historically, groups who are CMV donor positive and CMV recipient negative (CMV D+/R-) are at greatest risk for severe "primary" infection during the first 3 months post transplantation.

16. Besides infection, what other ways does CMV infection affect the transplant recipient?

CMV has been associated with atherosclerosis and chronic allograft rejection. CMV is associated with several other vascular injuries, including transplant glomerulopathy, hemolytic uremic syndrome, thrombotic microangiopathy, and transplant renal artery stenosis.

17. How do you diagnose CMV disease in a kidney transplant recipient?

CMV infection implies the detection of CMV via culture or PCR. By comparison, CMV disease requires clinical signs and symptoms, in addition to viral detection. The clinical signs and symptoms of CMV disease include fever, leukopenia, or organ involvement (hepatitis, pneumonitis, colitis, chorioretinitis, etc.). The quantitative assessment of viral load via PCR can help determine the clinical phenotype. CMV DNA levels >500 copies/mmg of total DNA in peripheral blood correlates with clinically evident disease.

18. What are the prophylactic strategies for CMV infection?

There are two strategies for CMV prevention; antiviral prophylaxis and preemptive monitoring/therapy. Antiviral prophylaxis means giving valganciclovir without any evidence of CMV infection or viremia. Preemptive monitoring/therapy means reserving antiviral therapy for patients who develop CMV viremia. Preemptive monitoring is associated with lower drug costs and adverse toxicities. However, there are increased laboratory surveillance and logistical labor. Antiviral prophylaxis, on the other hand, is more expensive and puts patients at risk for drug toxicity but is associated with decreased reactivation of other herpesvirus, lower rates of opportunistic infections, and allograft loss. The drug of choice for prophylaxis is valganciclovir. The duration of CMV prophylaxis depends on the CMV serology of the donor and recipient. D+/R- prophylaxis lasts 6 months, and all others last 3 months.

19. What is the treatment for CMV?

Ganciclovir and valganciclovir are the most commonly used agents for the treatment of CMV infection. Both drugys must be dosed based on renal function. Valganciclovir is indicated in patients with mild to moderate disease. The treatment dose with normal kidney function is 900 mg twice daily. The dose needs to be reduced in kidney failure. Ganciclovir is indicated in more severe disease, those with high viral load, or those with questionable gastrointestinal absorption. Treatment is usually continued until the viral load is undetectable for 2 weeks, then the patient is switched to 1 to 3 months of prophylactic therapy. If the viral load does not change with appropriately dosed ganciclovir after 2 to 3 weeks, then ganciclovir resistance should be assessed by viral genotype testing. If resistance is discovered, the usual strategy is to increase the ganciclovir dose or use foscarnet or cidofovir. However, these are nephrotoxic. The other aspect of treatment is the careful reduction of immunosuppression.

20. What is Epstein-Barr virus (EBV) and what posttransplantation condition is it associated with?

EBV is a member of the herpesvirus family and one of the most common human viruses. Most people become infected with EBV sometime during their lives. It can flourish in the setting of immunosuppression and is associated with PTLD.

21. Discuss vaccinations in reference to kidney transplantation.

Live vaccines are contraindicated after transplantation and should be administered prior. If a live vaccine is given prior to transplantation, the patient cannot be on immunosuppression and therefore transplanted for a minimum of 4 weeks. Inactivated vaccines can be given post transplant. The time frame to be able to receive a vaccination post transplant is 3 to 6 months. Close contacts should also be appropriately vaccinated. Table 60.1 shows a table of commonly questioned vaccinations.

The inhaled influenza vaccine is a live attenuated vaccine and is contraindicated. Patients traveling abroad should consider visiting a travel clinic for appropriate vaccinations and prophylaxis as needed.

Table 60.1. Vaccine Timing and Transplant

VACCINE	INACTIVATED/LIVE ATTENUATED	GIVE PRIOR OR AFTER TRANSPLANTATION
Influenza (injected)	Inactivated	Both
Hepatitis B	Inactivated	Both but preferably completed prior to transplant
Tetanus	Inactivated	Both
Pertussis (Tdap)	Inactivated	Both
Streptococcus pneumoniae	Inactivated	Both
Neisseria meningitidis	Inactivated	Both
Rabies	Inactivated	Both
Measles-Mumps-Rubella (MMR)	Live Attenuated	Only Prior
Varicella	Live Attenuated	Only Prior
Human Papilloma Virus	Inactivated	Both

22. Is hepatitis C treatable post kidney transplant?

Yes. Interferon alpha and ribavirin are contraindicated post transplant. Direct-acting antiviral agents (DAAs) can be used in the kidney transplant population with an estimated glomerular filtration rate >30 mL/min. This has also increased the use of hepatitis C–positive kidneys in transplantation, increasing the transplant rate. A patient with hepatitis C, if not overtly cirrhotic, can be listed for a hepatitis C kidney, which has a substantially shorter wait time. They are treated post transplant with DAAs. Studies are being developed to look at transplanting organs from Hepatitis C positive donors to hepatitis C negative recipients. The recipients would be treated for Hepatitis C posttransplant.

23. What are the requirements for a human immunodeficiency virus (HIV)-infected individual to qualify for a transplant?

Well-controlled HIV with CD4 counts >200 cells/mmL, undetectable viral load, and the absence of untreatable infection or malignancy. There must be great care taken in these patients because their antiretroviral medications have significant interactions with transplant medications.

24. What central nervous system infections are of particular concern in patients who have undergone solid organ transplant?

- Listeria meningitis
- Herpes simplex virus encephalitis
- JC virus–induced PML
- *Cryptococcus neoformans* meningitis

KEY POINTS

1. Nosocomial and surgery-related infections are the predominant infections that occur within the first month post transplantation.
2. Although the human polyomaviruses are highly seroprevalent in humans, they appear to cause clinical disease only in immunocompromised hosts.
3. The goal in treating BK-associated nephropathy is to eradicate the virus while maintaining kidney function and preventing acute or chronic rejection.
4. CMV-positive donor to CMV-negative recipient (CMV D+/R-) transplants are at greatest risk for severe "primary" infection during the first 3 months post transplantation. However, CMV D+/R+ group and not the D+/R- group has the worst graft and patient survival at 3 years. This could be secondary to increased vigilance in monitoring the CMV D+/- group.
5. Epstein-Barr virus can flourish in the setting of immunosuppression and is associated with the majority of posttransplant lymphoproliferative disorder.
6. Live vaccines are contraindicated post transplant.

Bibliography

Fishman, J. A. (2007). Infection in solid-organ transplant recipients. *New England Journal of Medicine, 357*(25), 2601–2614. doi:357/25/2601. [pii].

Jamboti, J. S. (2016). BK virus nephropathy in renal transplant recipients. *Nephrology (Carlton), 21*(8), 647–654. doi:10.1111/nep.12728.

Karuthu, S., & Blumberg, E. A. (2012). Common infections in kidney transplant recipients. *Clinical Journal of the American Society of Nephrology, 7*(12), 2058–2070. doi:10.2215/CJN.04410512.

Ramanan, P., & Razonable, R. R. (2013). Cytomegalovirus infections in solid organ transplantation: A review. *Infection & Chemotherapy, 45*(3), 260–271. doi:10.3947/ic.2013.45.3.260.

Sawinski, D., & Goral, S. (2015). BK virus infection: An update on diagnosis and treatment. *Nephrology Dialysis Transplantation, 30*(2), 209–217. doi:10.1093/ndt/gfu023.

Sawinski, D., Kaur, N., Ajeti, A., Trofe-Clark, J., Lim, M., Bleicher, M., . . . Bloom, R. D. (2016). Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. *American Journal of Transplantation, 16*(5), 1588–1595. doi:10.1111/ajt.13620.