4 Infectious diseases in transplantation

Robin K Avery[1] *and Jay A Fishman*[2]

[1]The Cleveland Clinic and Cleveland Clinic Lerner College of Medicine, USA
[2]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Management of infection in the immunocompromised transplant recipient is complicated by a variety of factors. These include increased susceptibility to a spectrum of infectious pathogens, the difficulty of recognizing infectious syndromes in the face of diminished signs and symptoms of inflammation, an array of non-infectious etiologies of fever (including graft rejection and drug toxicity), and the frequency with which multiple processes coexist. At the same time, immunocompromised patients tolerate poorly any delays in appropriate antimicrobial therapies, increasing the urgency for an early, specific diagnosis. As anti-rejection therapies are largely aimed at suppression of T-lymphocyte functions, viral infections, in particular, are increased. These contribute to the risk for other opportunistic infections, including those due to *Pneumocystis* and *Aspergillus* species, and for cancers mediated by viral infections.

Risk of infection

The risk of infection in the transplant recipient is determined by the interaction of two factors:
1. Epidemiologic exposures of the patient including those unrecognized by the patient or distant in time – including the organisms and the virulence, intensity and timing of infectious exposures (Table 4.1)

Primer on Transplantation, 3rd edition.
Edited by Donald Hricik.

2. The patient's net state of immunosuppression, including all the factors that contribute to the risk for infection such as the intensity and timing of exogenous immunosuppression, underlying conditions including metabolic disorders or neutropenia, the presence of vascular lines or other breaks in mucocutaneous barriers, and concomitant viral infections (Table 4.2).

Epidemiologic exposures

Knowledge of the details of an individual's epidemiologic history allows the clinician to establish a differential diagnosis for a given "infectious" presentation and to design the optimal preventive strategy for each patient. One aspect of this process relies on screening of the organ donor and the recipient (Tables 4.3 and 4.4). Key interventions that result from screening include empiric therapies for latent tuberculosis, *Strongyloides stercoralis* in patients from endemic regions, and patients who receive organs from donors discovered to have acute bacterial, viral, or fungal infections. Specific antiviral preventive strategies, notably for cytomegalovirus (CMV), are stratified according to individual risk for all transplant recipients.

Exposures of importance can be divided into four overlapping categories: donor- or recipient-derived infections, and community or nosocomial exposures.

Donor-derived infections
Infections that are derived from the donor tissues and cause invasive disease in the recipient are among the most important exposures in transplantation. Some of these are due to latent pathogens whereas

Table 4.1 Significant epidemiologic exposures relevant to transplantation

Donor derived	**Nosocomial exposures**
Viral	Methicillin-resistant staphylococci
Herpes group (cytomegalovirus, Epstein–Barr virus, human herpesviruses 6, 7, 8, herpes simplex virus)	Vancomycin-resistant enterococci (also linezolid and quinupristin–dalfopristin resistance)
Hepatitis viruses (notably B and C)	*Aspergillus* spp.
Retroviruses (HIV, HTLV-1 and -2)	*Candida* non-*albicans* strains
Others	**Community exposures**
Bacteria	Food and water borne (*Listeria monocytogenes*, *Salmonella* spp., *Cryptosporidium* spp., hepatitis A, *Campylobacter* spp.)
Gram-positive and Gram-negative bacteria (*Staphylococcus* spp, *Pseudomonas* spp., Enterobacteriaceae)	Respiratory viruses (respiratory syncytial virus [RSV], influenza, parainfluenza, adenovirus, metapneumovirus)
Mycobacteria (tuberculosis and non-tuberculous)	Common viruses – often with exposure to children (Coxsackie virus, parvovirus, polyomavirus, papillomavirus)
Nocardia asteroides	Atypical respiratory pathogens (*Legionella* spp., *Mycoplasma* spp., *Chlamydia* spp.)
Fungi	Geographic fungi and cryptococci, *Pneumocystis jiroveci*
Candida spp.	Parasites (often distant)
Aspergillus spp.	*Strongyloides stercoralis*
Endemic fungi (*Cryptococcus neoformans*)	*Leishmania spp*
Geographic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces* spp.)	*Toxoplasma gondii*
Parasites	*Trypanosoma cruzi*
Toxoplasma gondii	
Trypanosoma cruzi	

Table 4.2 Factors contributing to the "net state of immunosuppression"

Immunosuppressive therapy: type, temporal sequence, intensity
Prior therapies (chemotherapy or antimicrobials)
Mucocutaneous barrier integrity (catheters, lines, drains)
Neutropenia, lymphopenia (often drug induced)
Underlying immune deficiency, e.g.,
Hypogammaglobulinemia
Systemic lupus, complement deficiencies
Metabolic conditions: uremia, malnutrition, diabetes, alcoholism/cirrhosis
Viral infection (cytomegalovirus, hepatitis B and C viruses, respiratory syncytial virus)
Immunosuppression (indirect effects of viral infection)
Graft rejection
Cancer/Cellular proliferation

Table 4.3 The pretransplant evaluation (consider the following)

Laboratory test	All patients	Patients with exposure in endemic area	Quantitative viral studies available (PCR)
Serologies			
CMV	✓		✓
HSV	✓		✓
VZV	✓		
EBV	✓		✓
HIV	✓		✓
HBV: HBsAg, HBcAb	✓		✓
Anti-HBs	✓		
HCV	✓		✓
Treponema pallidum (RPR)	✓		
Toxoplasma gondii	✓		
Strongyloides stercoralis		✓	
Leishmania spp		✓	
Trypanosoma cruzi		✓	Blood smear
Histoplasma capsulatum		✓	
Cryptococcus neoformans		✓	Cryptococcal antigen
Coccidioides immitis		✓	
Cultures, etc.			
Urinalysis and culture	✓		
Skin test: PPD	✓		
Chest radiograph (routine)	✓		
Stool ova and parasites (*Strongyloides*)		✓	
Urine ova and parasites/Cystoscopy		✓ (for kidneys)	(Schistosomiasis endemic areas)

See the text for abbreviations. PPD, purified protein derivative.

others are the result of bad timing – active infection transmitted at the time of transplantation. The subsequent activation of infection may reflect the intensity of immunosuppression and/or results from the allogeneic response (graft rejection), which can activate latent viral pathogens. Given the risk of transmission of infection from the organ donor to the recipient, certain infections should be considered relative contraindications to organ donation. As transplantation is, in general, semi-elective surgery, it is reasonable to avoid donation from individuals with unexplained fever, rash, neurologic syndromes, or other infectious syndromes. Some of the common criteria for exclusion of organ donors are listed in Table 4.4.

Recipient-derived exposures

Infections in this category are generally latent infections activated in the setting of immunosuppression. Thus, a careful history of travel and exposures can guide preventive strategies and empiric therapies. Notable among these infections are tuberculosis, strongyloidiasis, viral infections (herpes simplex and varicella-zoster), histoplasmosis, coccidioidiomycosis, hepatitis B or C, and HIV. Immunization status should be ascertained and updated in advance of transplantation (tetanus, hepatitis B, childhood vaccines, influenza, pneumococcal vaccine, varicella-zoster). Dietary habits should also be considered including the use of well water (cryptosporidia), uncooked meats (*Salmonella* and *Listeria* spp.),

Key points 4.1 Common forms of donor-derived infection

- Donors who are bacteremic or fungemic at the time of donation – these infections (staphylococci, pneumococci, *Candida* sp., *Salmonella* spp., *E. coli*) tend to "stick" to anastomotic sites (vascular, urinary) and may produce leaks or mycotic aneurysms as well as infection of fluid collections and abscesses
- Donors who are viremic (often asymptomatic) at the time of donation – including herpes simplex virus, West Nile virus, rabies, arboviruses, and the hepatitis viruses. Viremia may also occur during respiratory viral infections, which might allow transmission from extrapulmonary organs
- Latent viral infections transmitted with the graft including cytomegalovirus (CMV) and Epstein–Barr virus (EBV) that are associated with particular syndromes and morbidity in the immunocompromised population (discussed in text). The greatest risk is from primary infection – organ recipients who are seronegative (immunologically naïve) receiving grafts from seropositive donors
- Bacterial or fungal colonization (e.g., in the lung transplant donor), which can become an invasive infection in the recipient
- Late, latent infections including tuberculosis which may activate many years after the initial exposure. The treatment of disseminated mycobacterial infection is often complicated by drug interactions or toxicities in the transplant recipient

or unpasteurized dairy products (*Listeria* spp.). Asymptomatic *Strongyloides stercoralis* infection may activate more than 30 years after initial exposure due to the effects of immunosuppressive therapy. Such reactivation can result in either a hyperinfestation syndrome (characterized by hemorrhagic enterocolitis, hemorrhagic pneumonia, or both) or disseminated infection with accompanying Gram-negative bacteremia or meningitis.

Community exposures

Common exposures may be related to contaminated food and water ingestion, exposure to infected children or co-workers, or exposures resulting from hobbies (gardening), travel, or work. Respiratory virus infection caused by influenza, parainfluenza, respiratory syncytial virus (RSV), or adenoviruses, or by more atypical pathogens (herpes simplex virus [HSV], herpes zoster virus [HZV]) carry a risk for viral pneumonia and subsequent bacterial or fungal superinfection. Community (social or transfusion-associated) exposure to cytomegalovirus (CMV) and Epstein–Barr virus (EBV) may produce severe primary infection in the non-immune host. Recent and remote exposures to endemic, geographically restricted systemic mycoses (*Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*) and *Mycobacterium tuberculosis* can result in localized pulmonary, systemic, or metastatic infection. Gastroenteritis due to *Salmonella* spp., *Yersinia* spp., or *Campylobacter jejuni* may result in more severe and prolonged diarrheal disease as well as the risk of bloodstream invasion and metastatic infection.

Case

A heart transplant recipient developed pulmonary nodules and was found on biopsy to have *Rhodococcus equi* infection. Although the patient owned no farm animals, she had walked through nearby fairgrounds where there were swirling hay dusts.

Nosocomial exposures

Nosocomial infections are of increasing importance because organisms with significant antimicrobial resistance predominate in many centers. These include vancomycin-, linezolid-, and quinupristin–dalfopristin-resistant enterococci, methicillin-resistant staphylococci, and fluconazole-resistant *Candida* spp. or *Aspergillus* spp. A single case of nosocomial aspergillus infection in a compromised host should be seen as an indication of a problem with infection control practices. Antimicrobial overuse and the emergence of an epidemic strain have resulted in increased rates of *Clostridium difficile* colitis. Outbreaks of infections due to *Legionella* spp. have been associated with hospital plumbing and contaminated water supplies or ventilation systems. Each nosocomial infection should be investigated to ascertain the source and prevent subsequent infections. Nosocomial spread of *Pneumocystis jiroveci* between immunocompromised patients has also been suggested by a variety of case series. Respiratory viral infections may be acquired from medical staff and should be considered among the causes of fever and respiratory decompensation in hospitalized or institutionalized, immunocompromised individuals.

Table 4.4 Infectious considerations in evaluation of deceased organ donors[a]

Viral infection or Viremia (untreated)
- Herpesviruses including acute Epstein–Barr virus (mononucleosis), herpes simplex, varicella-zoster, cytomegalovirus
- HIV infection (serologic or molecular assay or by history)
- Active measles, mumps, varicella-zoster virus, rubella infections
- Herpes simplex encephalitis or other encephalitis
- HTLV-I/-II (serologic and molecular assays difficult to interpret)
- Hepatitis A, B, or C
- Severe acute respiratory syndrome (SARS)
- West Nile virus infection; arbovirus infections (Eastern equine encephalitis virus, St Louis encephalitis, Japanese encephalitis virus, dengue, yellow fever) – active or diagnosed within 6 months
- Lymphocytic choriomeningitis virus (LCMV)
- Rabies
- JC polyomavirus virus infection
- Creutzfeldt–Jakob disease
- Active viral pneumonia: influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, metapneumovirus infections (may be lung-specific)

Fungal infection (active/untreated)
- *Cryptococcus neoformans* or *Aspergillus* species infection of any site
- Systemic fungal infection including candidemia
- Active or history of infection due to *Histoplasma capsulatum* or *Coccidoides immitis* (may be lung-specific)

Central Nervous System infection
- Undiagnosed infection of central nervous system (e.g., encephalitis, meningitis)
- Untreated bacterial or viral meningoencephalitis (including tuberculosis)

Parasitic infection (untreated)
- *Trypanosoma cruzi*
- *Strongyloides stercoralis*
- *Toxoplasma gondii*
- *Leishmania* spp.
- *Babesia* spp.
- *Malaria* spp.
- *Ehrlichia* spp.

Pneumonia (untreated or undiagnosed) or bacteremia
- *Mycobacterium tuberculosis*, untreated disseminated non-tuberculous mycobacteria
- Meningococcal infection
- Bacteremia or sepsis syndrome
- Syphilis
- Lyme disease
- Rickettsial infection
- *Pneumocystis jiroveci*

Multisystem organ failure due to overwhelming sepsis, toxic shock syndrome

Untreated intra-abdominal infection (e.g., peritonitis or gangrenous bowel)

[a]Must be considered in the context of the individual donor and recipient. Undiagnosed infection may provide a greater infectious risk than incompletely treated donor-derived infection. Therapy may be continued in the recipient.

Table 4.5 Immunosuppression and specific infections

Anti-lymphocyte globulins (lytic) and alloimmune response: activation of latent (herpes)virus (CMV, EBV), fever, cytokines
Plasmapheresis: encapsulated bacteria
Co-stimulatory blockade: Unknown so far
Corticosteroids: bacteria, PCP, hepatitis B and C, fungal infection
Azathioprine: neutropenia, papillomavirus?
Mycophenolate mofetil: early bacterial infection, B cells, late CMV?
Calcineurin inhibitors (cyclosporine/tacrolimus): enhanced viral replication (absence of immunity), gingival infection, intracellular pathogens
Rapamycin: excess bacterial infections in combination with current agents, idiosyncratic pulmonary interstitial pneumonitis

CMV, cytomegalovirus; EBV, Epstein–Barr virus; PCP, *Pneumocystis jiroveci* pneumonia.

Net state of immunosuppression

The net state of immunosuppression is a measure of all of the factors contributing to the patient's risk for infection (see Table 4.2). Specific immunosuppressive agents are associated with increased risk for certain infections (Table 4.5). Combinations of these agents may enhance this risk or cause toxicity (e.g., nephrotoxicity) and may further enhance risk.

Key points 4.2 The most notable components of the "net state of immunosuppression"

- Immunosuppressive therapies, including the dose, duration, and sequence of these agents
- Technical problems from the transplant procedure, resulting in fluid collections or devitalized tissue
- Vascular access or dialysis catheters and surgical drainage catheters
- Critical illness requiring ICU care, broad-spectrum antimicrobial agents, prolonged intubation
- Renal and/or hepatic dysfunction and metabolic abnormalities including hyperglycemia
- Viral co-infection

With the proliferation of newer anti-rejection agents, longitudinal assessment of the immune status of the recipient has been of increasing interest. Monitoring relevant to infection risk can involve quantitation of particular types of cells (e.g., absolute lymphocyte count, CD4:CD8 ratio, and B-lymphocyte count) or measurement of immunoglobulin levels. More recently, functional assays have been developed that measure lymphocyte binding (e.g., tetramers) or cellular responses (e.g., interferon-γ release) in response to specific or non-specific antigenic stimuli and provide an assessment of cellular immune function. Genomic studies can characterize gene expression associated with a "state of rejection" or infection. Such tests ultimately may provide some quantitative measure of the net state of immunosuppression.

Timeline of infection

The risk factors for infection, epidemiology, and immune status are continuous variables over time. When immunosuppressive regimens are standardized, specific infections vary in a predictable pattern depending on the time elapsed since transplantation (Figure 4.1). This pattern is a reflection of most of the recipients in whom the intensity of immunosuppression generally is decreased over time and for whom other risk factors are reasonably common (surgery/hospitalization, immunosuppression, acute and chronic rejection, emergence of latent infections, and exposures to novel community infections). Although this concept is useful, at any given center the pattern may shift when immunosuppression is altered (e.g., substituting sirolimus for calcineurin inhibitors, use of co-stimulatory blockade instead of antithymocyte globulin, and minimization or withdrawal of corticosteroids). The risk of infection will be further altered by increases in the immunosuppression for treatment of graft rejection, intercurrent viral infection, neutropenia (drug toxicity), graft dysfunction, or significant epidemiologic exposures (travel or food).

The timeline reflects three overlapping periods of risk for infection:

1. The perioperative period to approximately 4 weeks after transplantation

2. The "opportunistic infection" period 1–6 months after transplantation (depending, for example, on the

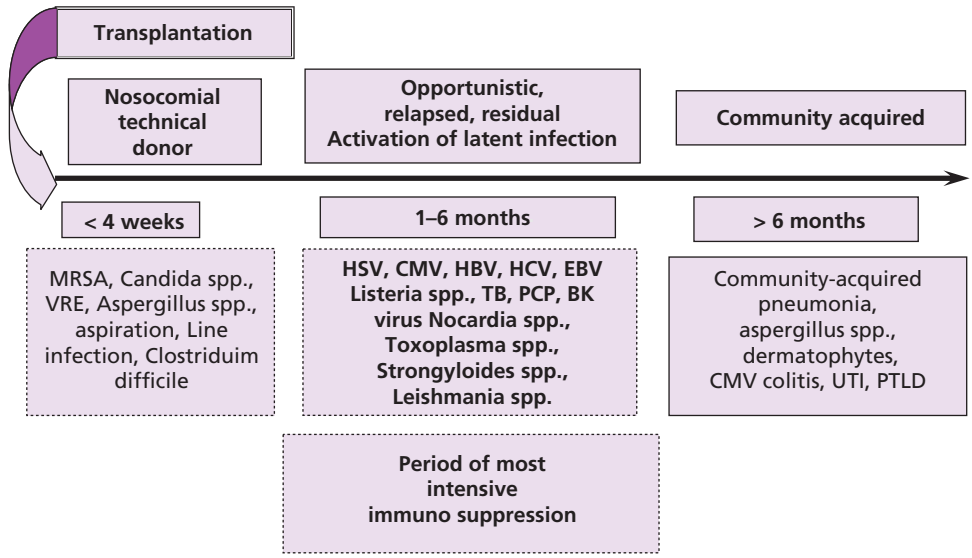

Figure 4.1 Timeline of post-transplant infections. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis jiroveci* pneumonia; PTLD, post-transplant lymphoproliferative disease; TB, tuberculosis; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus.

rapidity of taper of immune suppression and antibody-based "induction" therapies)

3. The period beyond 6 or 12 months after transplantation.

These periods reflect the changing major risk factors associated with infection: surgery and technical complications; intensive immunosuppression with viral activation; and community-acquired exposures and return to normal activities.

The timeline may be used in a variety of ways: to establish a differential diagnosis for the transplant patient suspected of having infection; as a clue to the presence of an excessive environmental hazard for the individual, either within the hospital or in the community; and as a guide to the design of preventative antimicrobial strategies. Infections occurring outside the usual period or of unusual severity suggest either excessive epidemiologic hazard or excessive immunosuppression.

Prevention of infection is linked to the risk for infection at various times after transplantation. Thus, the transplant recipient treated by plasmapheresis, or with hypogammaglobulinemia due to mycophenolate mofetil or azathioprine, requires enhanced protection against encapsulated bacteria (pneumococci, *Hemophilus influenzae*, meningococci) that may be provided by IgG replacement or trimethoprim–sulfamethoxazole. It should be noted that such strategies serve only to delay the onset of infection in the face of epidemiologic pressure. The use of preventive strategies (antimicrobial prophylaxis, vaccines) may only delay infection unless the intensity of immunosuppression is reduced or immunity develops.

Phase 1 (1–4 weeks post-transplant)

During the first month after transplantation, three types of infection occur:

1. The first type of infection is one that was present in the recipient before transplantation, was not eradicated, and emerges in the postoperative period. This may reflect, for example, untreated pneumonia or sinusitis, *C. difficile* colitis, or colonization with nosocomial pathogens. Control or eradication of such processes is an important part of preparation for transplantation.

2. The second type of early infection is transmitted from the infected donor to the recipient. This may be

nosocomially derived (resistant Gram-negative bacilli, *Staphylococcus aureus* or *Candida* spp.) due to either systemic infection in the donor (e.g., line infection) or contamination during the organ procurement process. Such patients are predisposed to abscesses around the allograft or to mycotic aneurysm at vascular suture lines. Donor-derived infections include tuberculosis (TB) or fungal (e.g., histoplasmosis) infections that emerge in the postoperative period before normal expectation. Recently, early donor-derived viral infections (lymphocytic choriomeningitis, rabies, West Nile virus) have also emerged in the first post-transplant month.

3. The third and most common type of infection in the early period is related to the complex surgical procedure of transplantation, and includes surgical wound infections, pneumonia (aspiration), bacteremia due to vascular catheters, urinary tract infections, or infected fluid collections at anastomotic sites, from bowel leaks, or of fluid collections. These infections are the result of nosocomial pathogens or endogenous flora and may be resistant to first-line antimicrobial agents. Given immune suppression, the signs of infection may be subtle and the severity or duration may be greater. *C. difficile* colitis is also common.

Notable by their absence in the first month after transplantation are opportunistic infections, even though the daily doses of immunosuppressive drugs are at their highest during this time. The implications of this observation are important: the net state of immunosuppression is not great enough to support the occurrence of opportunistic infections unless an exposure has been excessive. This observation suggests that it is not the daily dose of immunosuppressive drugs that is of importance but rather the sustained administration of these drugs (i.e., the "area under the curve") in determining the net state of immunosuppression. Thus, the occurrence of a single case of opportunistic infection in this period should trigger an epidemiologic investigation for an environmental hazard.

Phase 2 (1–6 months post-transplant)

Infection in the transplant recipient 1–6 months after transplantation has one of three causes:

1. Lingering infection from the postoperative period including relapsed *C. difficile* colitis, inadequately treated pneumonia, or infection related to a persistent technical problem (e.g., a urine or bile leak, lymphocele, hematoma).

2. Viral infections including CMV, HSV, shingles (varicella-zoster virus [VZV]), human herpesvirus 6 or 7, EBV, relapsed hepatitis (hepatitis B or C [HBV, HCV]). This group of viruses is unique because they induce life-long infection that is tissue associated (often transmitted with the allograft from seropositive donors or reactivated from past infection in the recipient). These viruses are also immunomodulating – systemically immunosuppressive (predisposing to opportunistic infection) – and, potentially, predispose to graft rejection. It is also notable that the herpes viruses are prominent due to the role of T-cell immune function in the control of these infections. Among the other viral pathogens of this period must be included BK polyomavirus in association with allograft dysfunction and community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, RSV, metapneumovirus). The suppression of antibody production (e.g., using tacrolimus and mycophenolate mofetil or with lymphopenia) may predispose to other infections.

3. Opportunistic infection due to *Pneumocystis jiroveci*, *Listeria monocytogenes*, *Toxoplasma gondii*, *Nocardia* spp., *Aspergillus* spp. (Figure 4.2), and other agents. In this category are pathogens endemic to specific regions including paracoccidioidiomycosis or Chagas' disease in South America, histoplasmosis in midwestern USA, and strongyloidiasis in recipients from south-east Asia.

In this period, the stage is also set for the emergence of a subgroup of patients – the "chronic n'eer do well" – individuals who require higher than average immune suppression to maintain graft function or who have prolonged, untreated viral infections and other opportunistic infections – predicting long-term susceptibility to many other infections (discussed below in phase 3). Such individuals may merit prolonged (life-long) prophylaxis (antibacterial and/or antiviral) to prevent life-threatening infection.

Phase 3 (>6–12 months post-transplant)

Transplant recipients who are more than 6 months post-transplant can be divided into three groups in terms of infection risk:

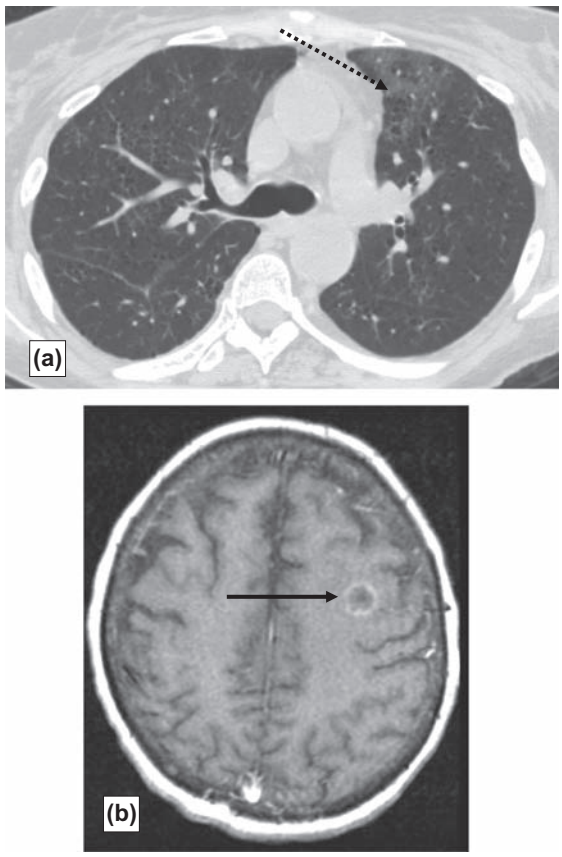

Figure 4.2 Liver transplant recipient with single colony of *Aspergillus fumigatus* in sputum and low-grade fever. She was otherwise asymptomatic. (a) Chest CT scan reveals patchy infiltrate (arrow). (b) Head CT scan reveals brain abscess (arrow) that was biopsied and grew *Aspergillus* sp. in culture.

1. The first group had a technically good procedure with satisfactory allograft function, tolerated reduction in immunosuppression, and lacked chronic viral infection. These patients resemble the general community in terms of infection risk, with community-acquired respiratory viruses constituting their major risk. Occasionally such patients will develop primary CMV infection (socially acquired) or infections related to underlying diseases (e.g., skin infections in diabetes).

2. The second group suffers the effects of persistent viral infections, which produces: – end-organ damage (e.g., BK polyomavirus nephropathy, cryoglobulinemia or cirrhosis from HCV) – malignancy (post-transplantation lymphoproliferative disease [PTLD] due to EBV, skin or anogenital cancer due to papillomaviruses).

3. The third group of patients is the "chronic ne'er do wells" who have less satisfactory allograft function and require more intensive immunosuppression. They are at risk for chronic viral infection and for opportunistic infections with *P. jiroveci*, *Listeria monocytogenes*, *Nocardia asteroides*, and *Cryptococcus neoformans*. Such patients require lifetime trimethoprim–sulfamethoxazole prophylaxis and are considered for antifungal prophylaxis. This group also develops the unusual infections of chronic immune deficiency such as *Nocardia, Rhodococcus*, *Cryptosporidium*, or *Microsporidium* spp., or invasive fungal pathogens (*Aspergillus* spp., or the families Zygomycetes, or Dematiaceae, or pigmented molds) (see Figure 4.2). Minimal signs of infection merit intensive evaluation in such high-risk individuals.

Pretransplant evaluation

Prospective donors and recipients undergo a panel of tests (see Table 4.3) to detect active or latent infections that may reactivate after transplantation. The specific organisms and conditions assayed are chosen by the Organ Procurement and Transplantation Network (OPTN) and are under review (a possible revised list is given in Table 4.4). These assays serve to establish the suitability of the donor or recipient and to stratify risk for common postoperative infections (e.g., CMV). Risk stratification is used to design appropriate post-transplant prophylactic strategies. Donor blood cultures are recommended if the donor has been hospitalized >72 h, and donor bronchial cultures for bacteria, fungi, and acid-fast bacilli (AFBs) are sent at the time of lung transplantation. A careful social and travel history may also provide clues to unsuspected exposures before seroconversion (e.g., HCV, HIV) or diagnosis (Chagas' disease).

Pre-transplant interventions in the recipient include updating of immunization status (Table 4.6) and initiation of treatment for strongyloides infection or latent TB. HBV immunization should be achieved in all recipients but may be especially important for

Table 4.6 Immunizations to consider before transplantation

Adult
Pneumococcal (if last dose >5 years ago)
Hepatitis B (if seronegative; consider accelerated or enhanced-potency series)
Td or Tdap booster (if last dose >5 years ago)
Varicella (if seronegative and >3 weeks before anticipated transplant)
Influenza – yearly, injected vaccine for both seasonal and novel H1N1 influenza
Completion of any unfinished pediatric vaccine series (see below)
Children
Diphtheria/tetanus/pertussis series
Hemophilus influenzae type b (Hib) series
Hepatitis B series
Conjugated or polysaccharide pneumococcal vaccine (see Guidelines)[a]
Varicella
Yearly influenza (injected vaccine, both seasonal and novel H1N1 influenza)
Meningococcal vaccine (adolescents or military recruits)
Live vaccines contraindicated in transplant recipients
Oral polio vaccine[b]
Varicella vaccine
Measles–mumps–rubella (MMR) vaccine
Smallpox vaccine
Oral typhoid vaccine[b]
Inhaled influenza vaccine (?await further data)

[a]Inactivated vaccines are acceptable.
[b]Oral polio is no longer used in the USA.

recipients of organs from HBV core-antibody-positive (HBsAg–, HBcAb+ [HBV surface antigen negative, HBV core antibody positive]) donors. Pretransplant cultures of colonizing respiratory organisms (such as *Pseudomonas* spp. in cystic fibrosis patients) are used to devise individualized peritransplant prophylaxis.

General principles in management of infectious syndromes

A number of concepts merit consideration in the management of infections in immunocompromised hosts:

- Diminished signs of infection are present in radiologic studies as well as in physical signs and symptoms. The use of computed tomography (CT) or magnetic resonance imaging (MRI) is essential for assessing the presence and nature of infectious and malignant processes.
- The "gold standard" for diagnosis is tissue histology. No radiologic finding is sufficiently diagnostic to obviate the need for this. Further, multiple simultaneous infections are common. Thus, invasive procedures to obtain pre-antimicrobial cultures or histology are a routine component of the initial evaluation of transplant recipients with infectious syndromes. Molecular assays are highly useful and

may be used to monitor the course of infection or therapy.

- Serologic tests (antibody assays) are useful in the pretransplant setting but are rarely of use for acute diagnosis after transplantation. Patients rarely seroconvert in a time frame useful for clinical diagnosis. Thus tests that detect proteins (e.g., enzyme-linked immunsorbance assay [ELISA], direct immunofluorescence for respiratory viruses) or nucleic acids (quantitative molecular assays) should be used.
- Antimicrobial resistance can be acquired during therapy and resistant organisms acquired during hospitalization. Sites at risk (ascites, blood clots, drains, lungs) must be sampled routinely to guide empiric therapy at times of clinical deterioration.
- Antimicrobial agents are of little use in the presence of undrained fluid collections, blood, or devitalized tissues. The use of antimicrobial agents in these settings merely delays clinical deterioration and promotes the acquisition of resistant microorganisms. Early and aggressive surgical debridement of such collections is essential for successful care.
- Resolution of infection is generally slower than in normal hosts. Thus, the course of therapy is usually longer and resolution must be documented – radiologically or via other assays.

Antimicrobial selection in the transplant recipient

There are four major principles of antimicrobial selection:

1. Obtain diagnostic samples for cultures and histology before initiating therapy

2. Initiate broad antimicrobial coverage with more focused therapy when culture results are available

3. Avoid agents with synergistic nephrotoxicity

4. Be aware of drug interactions (azoles, macrolides, rifampin).

Transplant recipients are susceptible to infections with a wide variety of pathogens. The clinical patterns at presentation are highly variable. Thus, specific microbiologic data are the key to ultimately successful therapy. To devise an early and empiric antimicrobial regimen, the timetable of infection, the net state of immunosuppression, center-specific antimicrobial susceptibility patterns, and environmental exposures can be utilized. After initial broad coverage, more focused coverage can be substituted when culture results are available. Unless no other choices are available, it is desirable to avoid nephrotoxic agents (aminoglycosides, amphotericin B, foscarnet) because their toxicity may be amplified in patients receiving cyclosporine or tacrolimus.

Drug interactions should always be considered. Macrolides (particularly clarithromycin and erythromycin) elevate levels of calcineurin inhibitors and can precipitate toxicity. Azithromycin can be used safely. Azole antifungals elevate levels of calcineurin inhibitors and sirolimus. Close monitoring of levels is required both when initiating and when discontinuing these agents. The transplantation center should always be informed when a macrolide or azole is started or stopped. Rifampin decreases calcineurin inhibitor levels and can precipitate rejection. If rifampin is necessary for treatment of TB or staphylococcal infection, discussion with the transplant team and careful monitoring are required.

Case

A heart transplant recipient developed symptoms of bronchitis and was started on clarithromycin at an urgent care center. The transplant team was unaware. Several days later he was admitted with a high cyclosporine level and a serum creatinine of 4.0 mg/dL from cyclosporine toxicity. Renal function improved when clarithromycin was discontinued and the cyclosporine level fell to the normal range.

Special considerations after transplantation

Postoperative infections

Postoperative infections are frequently related to technical complications of the transplantation itself, such as bleeding, urine leaks, or lymphoceles in kidney recipients, or bile leaks in liver recipients. Wound infections in abdominal transplant recipients may involve mixed pathogens, including enteric organisms such as enterococci and Gram-negative aerobes, *Candida* spp., and anaerobes (notably in people with diabetes) as well as skin-derived *Staphylococcus* spp. and streptococci. Although wound infections may complicate thoracic transplantation, heart or lung recipients often develop pneumonias and occasionally

empyema. In heart recipients with prior ventricular-assist devices (VAD), preoperative VAD-related infections may persist (see below).

Antimicrobial resistance

In recent years, an increase in infections due to bacteria and yeasts carrying antimicrobial resistance has been observed. The challenge of these pathogens includes: development of newer antibiotic therapies; infection control measures including judicious use of antibiotics; and management of donor or recipient colonization.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of catheter-related bacteremias, wound infections, and ventilator-associated pneumonias, and is associated with a high mortality. Bacteremic seeding may occur, resulting in endocarditis, osteomyelitis, and septic thrombophlebitis with pulmonary emboli. In the immunocompromised host, recurrences after apparently successful therapy are more common than in the normal host. No intervention has consistently prevented post-transplant MRSA infections, although decreased colonization may be attempted in some patients with topical nasal application of mupirocin ointment with or without systemic antimicrobial therapy.

Vancomycin-resistant *Enterococcus faecium* and *faecalis* (VRE) infections are increasing among dialysis and liver transplant recipients and are associated with a high mortality. Such organisms are resistant to vancomycin and, in general, to ampicillin, with variable susceptibility to aminoglycosides (gentamicin) and macrolides (tetracycline). VRE infections are seen as a marker of the overall illness of the patient rather than as a direct causal factor in mortality. Invasive infections due to VRE generally occur in patients colonized with VRE. Thus far, there are no effective therapies to decolonize the gastrointestinal tract. Treatment of susceptible strains with gentamicin may be complicated by nephrotoxicity in transplant recipients receiving calcineurin inhibitors. In vitro susceptibility data (e.g., to chloramphenicol) may be misleading. Newer agents (e.g., linezolid, quinupristin–dalfopristin, daptomycin) have improved outcomes, but resistance to these agents is emerging also, side effects of therapy are common, and morbidity remains high. Multiresistant Gram-negative bacilli including *Pseudomonas* spp. and extended-spectrum β-lactamase-producing (ESBL) *E. coli* and *Klebsiella* spp., and carbapenemase-producing *Acinetobacter* and *Klebsiella* spp. may colonize patients after multiple courses of antimicrobial agents (e.g., recurrent pneumonia in cystic fibrosis or chronic cholangitis) or after prolonged ICU stays. Therapy must be guided by antimicrobial susceptibility patterns and documentation of the presence of invasive infection – colonization cannot be cleared in such patients and therapy may only breed further resistance. In the absence of the radiologic demonstration of pneumonia, cultures of colonized upper airways may be misleading in terms of the need for systemic antimicrobial therapy (e.g., sputum Gram stains without organisms or neutrophils). Adjunctive therapies may be added to standard antimicrobial agents including therapeutic bronchoscopic lavage, repletion of hypogammaglobulinemia, treatment of concomitant viral infections, or the use of inhaled colistin. When resistance to standard antipseudomonal drugs occurs, in vitro antimicrobial synergy studies may provide therapeutic alternatives.

Over half of the *Candida* spp. isolated in most US medical centers are now non-*albicans* strains. As a result, infections may be due to fluconazole-resistant yeast (e.g. many *C. glabrata* and all *C. krusei*). Assessment of fluconazole susceptibility should be performed for all yeasts isolated form sterile sites (blood, abdomen). Such isolates may be treated with echinocandins, later generation azoles (if susceptible), or amphotericin-based products.

Infections relating to vascular devices

Infections can be associated with temporary catheters, or indwelling access such as PICC lines or Hickman catheters. Four major forms of catheter-related infection include: exit site; tunnel infection (which requires catheter removal); bacteremia without external signs; and septic thrombophlebitis. Common pathogens include coagulase-negative staphylococci, *Staphylococcus aureus*, and occasionally Gram-negative bacteria and yeasts. Infections are generally managed by catheter removal and antibiotic therapy (although coagulase-negative staphylococcal infection can often be treated with the catheter in place.).

VADs may be in place for months and carry a high risk of infection. Often the drive-line exit site is the initial focus but may progress to bacteremia. Sequential infections with different pathogens are

common. Resolution of the infection requires removal of the VAD at the time of transplantation plus ongoing post-transplant antibiotic therapy.

Pneumonia

Pneumonia in transplant recipients falls into three overlapping categories: nosocomial, community acquired, and opportunistic. In the early post-transplant period, transplant recipients may develop nosocomial pneumonias following aspiration or due to *S. aureus* and Gram-negative bacilli. The spectrum of pathogens is broader in the setting of lung transplantation, with prolonged hospitalization or with early graft dysfunction requiring intensive immune suppression (*Aspergillus* spp. and other fungi). Community-acquired respiratory viruses may be acquired (from staff or visitors) while hospitalized, be complicated by superinfection, and provoke lung rejection or progress to respiratory failure. These are often detected by rapid screens (e.g., nasal swab with immunofluorescence). At any time after discharge, pneumococci, and *Legionella*, *Mycoplasma*, and *Chlamydia* spp. may also cause infection. Opportunistic pathogens are most likely to cause pneumonia in the second post-transplant period when the patient is most highly immunosuppressed. Radiographic patterns, particularly on chest CT, are helpful. Nodular infiltrates, particularly if cavitating, suggest fungal or mycobacterial infection, or nocardiosis. The "halo sign" is suggestive of aspergillosis, but virtually any pattern may be seen with these infections. Rapid progression to multilobar pneumonia suggests organisms such as *Legionella* spp., *S. aureus*, or Gram-negative bacilli. Diffuse infiltrates suggest *Pneumocystis* spp. or viral infection. Pulmonary–CNS infections are most often observed with *Aspergillus* and *Nocardia* spp., cryptococci, members of Zygomycetes (*Mucor* spp. in the sinus and lung).

Transplant recipients with pneumonia merit urgent evaluation including history, physical examination, chest radiograph, blood and urine cultures, sputum for Gram stain, bacterial, fungal, and mycobacterial cultures, nasal swab for a respiratory viral panel, and consideration for early chest CT and bronchoscopy. Induced sputum examinations are most useful for the diagnosis of mycobacterial infection, pneumocystis pneumonia, and malignancy. Epidemiologic clues may suggest further studies including, urine for pneumococcal, legionella (pneumophila) and histoplasma antigens, serum cryptococcal antigen, galactomannan or β-glucan assays (less useful in transplant recipients than cancer patients). Antimicrobial therapy should not be delayed while awaiting culture data. Antimicrobial resistance patterns in the community and any prior antimicrobial therapies should be considered when selecting empiric therapies.

The history may provide useful clues to diagnosis: prior viral syndromes may suggest bacterial (staphylococci) or fungal (*Aspergillus* or *Pneumocystis* spp.) superinfection. The introduction of sirolimus may suggest non-infectious infiltrates. "Intolerance" of prophylaxis or marked hypoxemia may suggest pneumocystis infection. Travel to endemic areas may suggest histoplasma or coccidioides infections. Gardening may predispose to *Aspergillus* or *Nocardia* spp.; gastrointestinal syndromes are common with sepsis, pneumococcal infection, or legionellosis.

CT scans of the chest are useful when the chest radiograph is negative or when the radiographic findings are subtle or non-specific. CT defines the extent of the disease process and the selection of optimal invasive techniques to achieve microbiologic diagnosis. Atypical CT findings may suggest the presence of dual or sequential infections of the lungs which are common in transplant recipients. Expectorated sputum is often non-diagnostic. Bronchoalveolar lavage (BAL) is often helpful with a microbiologic panel including assays for *Pneumocystis jiroveci* pneumonia, bacteria, fungi, mycobacteria, *Legionella* spp., CMV, HSV, *Nocardia* spp., and respiratory viruses. Transbronchial biopsy is a useful tool in making an etiologic diagnosis and to distinguish colonization (or rejection in lung recipients) from invasive infection. In some cases when diagnosis is elusive, open-lung biopsy provides a larger tissue sample.

Nocardia spp.

Nocardia infection is most common in thoracic transplant recipients and may involve the lungs, CNS, and other sites. The classic radiographic pattern is pulmonary nodules with associated infiltrates. Trimethoprim–sulfamethoxazole prophylaxis, when given three times weekly or daily, provides partial but not complete protection. Therapy may include high-dose trimethoprim–sulfamethoxazole, imipenem, amikacin, linezolid, ceftriaxone, or combinations. Antimicrobial susceptibility testing is useful to guide therapy.

Legionella spp.

Legionella spp. can cause a rapidly progressive, multilobar pneumonia in transplant recipients. Nosocomial acquisition may occur from hospital water systems. The microbiology laboratory should be notified when *Legionella* sp. is suspected because it requires special stains and culture media. Therapy is generally with a macrolide (azithromycin) or quinolone.

Mycobacterial infection

TB is a major concern in endemic areas, where up to 15% of patients reactivate after transplantation with a mortality rate as high as 50%. Graft loss may result from rifampin-containing regimens (which lower calcineurin inhibitor levels and may lead to rejection). Pre-transplant PPD screening (or TB interferon-γ release assay) and isoniazid prophylaxis of latent TB infection can reduce these risks, and prophylaxis started pretransplantation can be completed post-transplantation. Recent results suggest that isoniazid is generally well tolerated in this population with careful monitoring for hepatotoxicity.

Non-tuberculous mycobacterial infection (NTBI) may cause pulmonary or disseminated disease, particularly in lung transplant recipients. NTBI is included in the differential diagnosis of diffuse lymphadenopathy with lymphoma and other malignancy, TB and nocardiosis, histoplasmosis, acute viral infections (CMV and EBV), toxoplasmosis, and others. Antimicrobial regimens containing three or more drugs for 12 months or longer are generally used in treatment.

Intra-abdominal infection and *Clostridium difficile*

Intra-abdominal infections are most common in the kidney, liver, pancreas, or intestinal transplant recipient and are often related to technical problems. The most common organisms include Gram-negative bacilli, enterococci, anaerobes, and *Candida* spp., but staphylococci may also be seen. Management usually involves drainage (CT guided or surgical) and pathogen-directed antibiotic therapy.

Underlying anatomic problems must also be addressed. Pancreatic leaks may require revision of the bowel or bladder anastomosis, whereas biliary strictures or leaks may require dilation, stenting, or revision. Necrotic tissues may need debridement (e.g., after hepatic artery thrombosis). Urinomas and lymphoceles may require repair or drainage. Serial CT scans may be useful in determining the duration of antimicrobial therapy.

C. difficile is a toxin-producing organism that causes pseudomembranous colitis, generally following antimicrobial therapy. Any agent may predispose to this infection, but prolonged or broad-spectrum antimicrobial therapy and clindamycin are most often associated with it. Recently, a relatively virulent strain of *C. difficile* has emerged that carries increased risk for toxic megacolon and the need for colectomy. Preventive measures include stringent infection control and prudent use of antibiotics. *C. difficile* should be suspected in any patient with abdominal dilation or pain, fever, and leukocytosis, with or without diarrhea. Therapy is with oral metronidazole or oral vancomycin, or intravenous metronidazole if ileus is present. Probiotic agents (e.g. *Lactobacillus acidophilus*) as an adjunctive measure have been reported in nonrandomized trials to be helpful in preventing recurrences. CMV colitis must be considered in the differential.

Urinary tract infections

Urinary tract infections are most common in the kidney or kidney–pancreas transplant recipient with altered ureteric drainage and in whom graft pyelonephritis may be accompanied by graft dysfunction and bacteremia. The most common pathogens associated with urinary tract infections are Gram-negative bacilli and enterococci, often with significant antimicrobial resistance. Ultrasonography is useful to rule out hydronephrosis and peritransplant collections.

Urinary tract candidiasis is common early post-transplantation and may lead to upper-tract infection and fungemia. In non-kidney recipients, recurrent urinary tract infections should prompt an evaluation for possible anatomic abnormalities or persistent foci. Graft pyelonephritis is a potentially life-threatening infection and requires prolonged therapy (≥3 weeks) with effective agents. Cure of infection must be documented before cessation of therapy.

Central nervous system disease

The presentation of fever and headache, seizure, altered mental status, or other signs of CNS infection in organ transplant recipients is a medical emergency. The presentation of CNS infection may be obscured

Table 4.7 Neurologic infectious syndromes in transplant recipients

Presentation	Common pathogens	Other considerations
Acute meningitis	*Listeria* spp.	Pneumococci, meningococci, bleed
Subacute-on-chronic meningitis	Cryptococci	TB, cancer (PTLD), HSV, *Nocardia*, *Histoplasma*, and *Coccidioides* spp., brain abscess
Focal neurologic deficit Seizure/cerebritis	*Aspergillus* spp.	*Nocardia* spp., cancer (EBV-PTLD), bacterial brain abscess, bleed/ischemic, toxoplasma, vasculitis
Dementia	PML (JC virus)	Toxic drug effects, demyelination, HSV, CMV

See text for abbreviations.

by immunosuppression; signs of associated meningeal inflammation may be absent and changes in the level of consciousness may be subtle. A differential diagnosis is developed based on the neurologic deficits, brain imaging studies, and the temporal development of disease (Table 4.7). All transplant recipients with CNS syndromes require imaging and lumbar puncture for Gram stain, cell count, differential, glucose and protein, cryptococcal antigen, polymerase chain reactions or PCRs (which may include HSV, HHV-6, VZV, CMV, EBV, and JC virus), VDRL, routine bacterial, fungal and mycobacterial cultures, and viral cultures. Ideally, a tube of cerebrospinal fluid (CSF) is saved for subsequent testing (e.g., toxoplasma antibodies or PCR, aspergillus PCR, others).

Four main patterns of CNS infection are recognized in transplant recipients (but are not mutually exclusive):

1. Acute meningitis, usually caused by *Listeria monocytogenes* or pneumococci, less often by HSV

2. Subacute-to-chronic meningitis (fever and headaches evolving over several days to weeks, sometimes with altered state of consciousness) usually caused by *Cryptococcus neoformans*, but also with systemic infection with *M. tuberculosis*, *Listeria* spp., *Histoplasma capsulatum*, *Nocardia asteroides*, *Strongyloides stercoralis*, *Coccidioides immitis*, HSV, and EBV-associated PTLD

3. Focal brain infection, presenting with seizures or focal neurologic abnormalities, caused by *L. monocytogenes, T. gondii,* or *N. asteroides*; occasionally nodular vasculitis with infarction due to CMV or VZV, and occasionally with EBV-associated PTLD, but most commonly due to metastatic *Aspergillus* spp. or other invasive fungal infection (often with lung infection)

4. Progressive dementia (± focal processes) related to progressive multifocal leukoencephalopathy (JC polyomavirus), or with other viral infections or the toxic effects of calcineurin inhibitors, often in combination with metabolic or other drug effects.

Viral infections

The impact of viral infections includes direct infectious syndromes, and indirect effects including increased risk for other opportunistic infections and, in general, an increased risk for graft rejection or malignancy. Most important viruses are now diagnosed using quantitative assays, primarily molecular amplification techniques (PCR or similar), or protein detection tests such as the CMV pp65 antigenemia assay. The treatment of viral infections is largely reliant on a reduction in the intensity of immunosuppression. Antiviral agents are not available or very effective for many pathogens, and viral clearance depends on the emergence of host immune function.

Cytomegalovirus

CMV, a member of the herpesvirus family, is common in the general population and remains latent throughout life. CMV can be transmitted from the donor to the recipient or reactivated in the seropositive recipient, particularly after intensification of

immunosuppression. The donor seropositive and recipient seronegative (immunologically naïve) combination or "D+/R–" represents the highest risk category. Activation of CMV is stimulated by graft rejection, fever, and the use of depleting antilymphocyte antibodies among other factors. The clinical spectrum of CMV includes asymptomatic viremia, "CMV syndrome" (a flu-like illness with fevers, chills, myalgias, leukopenia, thrombocytopenia, and mildly elevated liver function tests), and tissue-invasive CMV (CMV pneumonitis, esophagitis, gastritis, colitis, hepatitis, retinitis, or other.) Symptomatic forms of CMV are generally associated with higher viral loads. CMV activation is often associated with activation of other viruses (human herpesviruses or HHV-6, -7, -8, or EBV), which is referred to as the "herpesvirus syndrome". CMV also predisposes to other opportunistic infections including those caused by *Aspergillus* and *Pneumocystis* spp., EBV-mediated lymphoma, accelerated atherogenesis after heart transplantation, and accelerated hepatitis C infection after liver transplantation. The diagnosis of CMV infection is by quantitative molecular assays or antigenemia assay. The molecular assays are more sensitive. Both may be negative in the face of invasive disease of the gastrointestinal tract or CNS.

The optimal approach to the prevention of CMV infection is controversial. The highest risk recipients (D+/R–) are generally treated for 3–6 months with antiviral prophylaxis (ganciclovir or valganciclovir, although CMV hyperimmune globulin and aciclovir and derivatives are also effective). Most of the lowest risk individuals (D–/R–) receive anti-HSV/VZV prophylaxis against cold sores and herpes zoster. The best approach to the seropositive recipient remains under investigation. The central question is whether prevention of asymptomatic viremia is useful. Recent analyses suggest that routine or "universal" prophylaxis is useful in reducing the risk for graft rejection as well as bacterial and fungal infections and PTLD. Prophylaxis is associated with higher drug costs and toxicities, and CMV infection may occur after the completion of prophylaxis (risk determined largely by the level of immunosuppression at that time). Preemptive therapy relies on serial monitoring and restricts antiviral therapy to those who develop viremia.

The treatment of CMV syndromes or invasive infection often includes a reduction in the intensity of immunosuppression with antiviral therapy. Traditionally, therapy for active CMV viremia was intravenous ganciclovir. A randomized trial of 3 weeks of intravenous ganciclovir versus oral valganciclovir therapy, followed by 4 weeks of oral valganciclovir, established the validity of treatment with oral valganciclovir in all but the most seriously ill patients. Regardless of the agent used, recurrences may occur. Ganciclovir-resistant CMV may develop, usually in the setting of the D+/R– combination, and particularly in the setting of subtherapeutic antiviral treatment (therapy or prophylaxis) and higher-intensity immunosuppression with higher viral loads. Alternative agents (e.g., foscarnet and cidofovir) are often nephrotoxic in combination with the calcineurin inhibitors (and have other toxicities) and the outcome of therapy for resistant CMV may be disappointing. Combination therapy using reduced-dose ganciclovir with foscarnet may be effective with reduced toxicity. Leflunomide has also been found to have a novel anti-CMV effect. CMV hyperimmune globulin may be used as an adjunct to therapy.

Herpes simplex virus and varicella-zoster virus

HSV may cause fever, malaise, and oropharyngeal or perineal ulcerations, especially in the early post-transplant period in patients not receiving CMV or other antiviral prophylaxis. HSV encephalitis (above) is one of the common forms of CNS infection in the immunocompromised host. Diagnosis of HSV encephalitis can be by viral cultures of CSF but more often is by HSV PCR from CSF.

VZV causes chickenpox (varicella), with reactivation from latency in neurons producing zoster (shingles). Primary chickenpox in the transplant recipient may cause pneumonia and fatal infection often due to bacterial or fungal superinfection. Pretransplant immunization of the seronegative candidate is desirable. Seropositive individuals (approximately 90% of adults) may reactivate VZV to develop zoster (shingles), which can be either dermatomal (localized) or disseminated (across multiple dermatomes or with systemic spread). Disseminated zoster may present with or without rash and skin pain, abdominal pain (cholangitis or hepatitis), pneumonitis, and/or CNS signs. Diagnosis is by viral culture of skin or other lesions, by immunofluorescence of slides prepared from active lesions, or Tzanck prep looking for multi-

nucleated giant cells with viral inclusions. Therapy is generally with high-dose aciclovir or ganciclovir.

Epstein–Barr virus

EBV causes a variety of syndromes in the transplant recipient including fever and neutropenia, lymphocytosis, lymphadenopathy (i.e., "infectious mononucleosis"), splenomegaly, hepatitis, meningoencephalitis, and PTLD. The risk for these syndromes is greatest in seronegative recipients of seropositive organs (EBV D+/R–, especially in children), with intensive immunosuppression with antilymphocyte therapies or primary infection – often in adolescent recipients. As with all herpesvirus infections, viral replication is controlled in the normal host by virus-specific cytotoxic T lymphocytes. In the presence of immunosuppression, viral activation results in uncontrolled replication of EBV and B-lymphocyte infection with subsequent transformation of EBV-infected lymphocytes. EBV-associated PTLD is generally of B-cell origin but may be T-, NK-, or null-cell derived. Tumors may infiltrate the graft or CNS or present with mass lesions, pulmonary nodules, gastrointestinal or tonsillar bleeding, or lymphadenopathy.

The diagnosis of PTLD requires histopathology and studies for genetic rearrangements (immunoglobulin genes), cell phenotyping (CD20, monoclonality), and anatomic distribution. Low-grade forms of PTLD are polyclonal lymphoproliferative processes that may respond to cellular immunity stimulated by intensive reversal of immunosuppression (that risks graft rejection). With transformation to monoclonal malignancy, immune responsiveness disappears and alternate therapies (rituximab for CD20+ tumors, chemotherapy, surgery, or radiotherapy) are used. CNS disease is poorly responsive and generally requires radiotherapy. Prevention of PTLD is sometimes attempted with antiviral prophylaxis (ganciclovir and aciclovir) and monitoring of EBV DNA viral loads with reduction in immunosuppression early in the course of disease.

Other herpesviruses: HHV6, HHV7, HHV8

Other herpesviruses (HHV-6, -7, and -8) may reactivate after transplantation, or may be acquired from the donor (particularly HHV-8). HHV-6 and -7 are the causes of roseola in infants, and can cause post-transplant pneumonitis, hepatitis, meniningoencephalitis, and myelosuppression. HHV-8 (KSHV) is the cause of Kaposi's sarcoma. There is currently no specific antiviral therapy for HHV-8. HHV-6 may be treated with ganciclovir or foscarnet.

BK polyomavirus

BK virus (BKV) is a member of the polyomavirus family and is associated with ureteric obstruction and/or progressive allograft nephropathy (BKVAN) and graft loss in renal transplant recipients. This syndrome rarely affects extrarenal transplant recipients. A related virus, JC, causes progressive multifocal leukoencephalopathy (PML). BKV infection is common in adults with latent virus residing in the uroepithelium. After kidney transplantation, viral activation may occur producing interstitial nephritis and fibrosis with allograft nephropathy. BKVAN is most often associated with intensive immunosuppression, including pulse dose steroid therapy for rejection, and possibly renal ischemia–reperfusion injury. Diagnosis is made by histopathology in the setting of progressive renal allograft dysfunction, with intracytoplasmic and intranuclear inclusions demonstrated in uroepithelial cells, viral crystalline arrays by electron microscopy, or immunostaining for cross-reacting SV40 large T antigen. Molecular assays (quantitative BK DNA PCR) of blood and urine (quantitative BK RNA PCR) have also been used both to adjust immunosuppression and to monitor response to therapy.

There is no specific therapy for BKVAN. Patients may stabilize or improve with reduction of immunosuppression. Studies of low-dose cidofovir and intravenous polyclonal immune globulin have shown inconsistent benefit whereas leflunomide is under study for adjunctive therapy. Molecular screening (e.g., serum BKV quantitative PCR every 3 months for the first year or for any unexplained rise in serum creatinine) and early intervention (reduced immune suppression) is highly recommended. In the screening era, the incidence of graft loss due to BKVAN has markedly decreased.

Hepatitis

The management of hepatitis viruses is covered in detail in Chapter 10. In addition to the risk of recurrent disease after liver transplantation, hepatitis

viruses may occur in non-hepatic transplant recipients, either as pre-existing infection in the recipient or as donor-acquired new infection. Hepatitis infection is often exacerbated in the setting of the treatment of graft rejection. Reactivation may be early and fulminant, or later and slowly progressive. Management issues are complex. It is worth noting that exacerbation of hepatitis may occur in the setting of concomitant viral infections such as CMV or EBV. The interaction between liver graft rejection and hepatitis remains to be defined. In HIV-infected individuals undergoing liver transplantation, hepatitis C may have a more rapid progression than in uninfected individuals even in the absence of detectable HIV.

Human papillomavirus

Human papillomavirus (HPV) is an increasing problem, particularly in long-term survivors of organ transplantation. Certain HPV types are associated with skin, cervical, and anal warts, and squamous cell cancers. Transplant recipients should undergo regular dermatologic examinations and should wear sun protection outdoors. Female recipients should have frequent screening pelvic exams and pap smears. Occasionally HPV may cause giant condylomatous lesions which can cause urethral or anal obstruction.

Parvovirus

Parvovirus B19, "fifth disease," is a common virus of childhood manifested by a "slapped-cheek" rash. Receptors for parvovirus are ubiquitous and present in the myocardium and on erythrocyte precursors. As a result, in immunocompromised hosts, parvovirus causes a variety of clinical syndromes including rash and fever, severe anemia unresponsive to erythropoietin, myocarditis, and pneumonitis. Serologic testing for parvovirus is often misleading and diagnosis should be made by quantitative DNA PCR for the virus. The treatment of choice is intravenous immunoglobulin (IVIG) with reduced immunosuppression. Multiple courses of therapy may be needed.

Case

A 37-year-old patient was admitted for a hemoglobin of 5.5 g/dL 6 months after a renal transplantation and despite erythropoietin therapy. Evaluation showed normal vitamin B_{12}, folate, and iron levels but a low reticulocyte count. Bone marrow biopsy showed giant pronormoblasts and serum DNA PCR assay was positive for parvovirus B19. The patient was treated with several doses of IVIG and recovered.

Community-acquired respiratory viruses

Influenza, parainfluenza, adenovirus, and RSV can all cause severe respiratory illness that may be complicated by superinfection (bacterial or fungal), enduring pulmonary dysfunction, or respiratory failure. All can be diagnosed in symptomatic individuals using rapid antigen detection assays (nasopharyngeal swabs) as well as cultures or molecular assays. Influenza and RSV are most common in the winter and early spring. These viruses are highly contagious, and require full respiratory isolation for hospitalized patients and contribute to bronchiolitis obliterans in lung transplant recipients. Yearly influenza immunization of transplant recipients is recommended, but immunization of healthcare workers and family members is also important. Recently, the novel H1N1 influenza virus has spread rapidly within the general population and poses a threat to immunocompromised patients. Immunization of all transplant recipients and candidates against seasonal and novel H1N1 influenza is recommended. As a result of increasing rates of resistance to antiviral agents in both seasonal and novel H1N1 influenza, it is recommended to follow the most recent treatment guidelines from the Centers for Disease Control and Prevention at www.cdc.gov/flu/professionals.

The use of aerosolized (and some intravenous) ribavirin has been described in patients with RSV or parainfluenza although there is no consensus on efficacy.

West Nile virus, rabies, lymphocytic choriomeningitis virus

West Nile virus (WNV) is a mosquito-borne flavivirus infection occurring in the summer and early fall. Transplant recipients are at increased risk of encephalitis, flaccid paralysis, and coma. There is no specific antiviral therapy. Transplant recipients should be given instructions on prevention (wearing insect repellent, staying inside at dawn or dusk when mosquitoes are feeding, clothes that cover arms and legs,

eliminating standing water sources). In addition, organ donor-derived WNV infection has been described with fatal outcome. Screening recommendations for deceased organ donors are evolving.

Recent reports of fatal donor-transmitted rabies and lymphocytic choriomeningitis virus (LCM) represent highly unusual occurrences. Most rabies in the USA is bat associated. LCM is a rodent-associated virus that is endemic in rodents including mice and hamsters. In recent cases of donor-derived infections, concomitant CNS events may have masked development of diagnostic neurologic signs of infection. It is reasonable to exclude as donors individuals with unexplained and/or untreated encephalitis or neurologic disease.

Fungal infections

Risks for fungal infections are often organ specific and also relate to external environmental exposures. Prophylaxis may be considered in certain high-risk groups. Risks for fungal infections include prolonged intubation or intensive care unit (ICU) stays, extensive blood transfusions, significant metabolic or graft (pulmonary, hepatic, renal, or diabetes) dysfunction, and re-exploration in the early post-transplant period.

Yeast infections

Candida infections are often line or catheter related and are most common in liver, pancreas, and intestinal transplant recipients. Risk factors in addition to those above include exposures to multiple antibiotics, technical difficulties (pancreatic leak, enterotomies), and renal dysfunction. Prophylaxis with fluconazole or liposomal amphotericin B has been advocated for high-risk patients but practice varies.

Cryptococcosis is of greatest impact in the CNS but can also cause pneumonia and pulmonary nodules, cellulitis and nodular skin lesions, or disseminated disease. Cryptococcal meningitis may be associated with obstruction of the fourth ventricle, increased intracranial pressure, and the need for CSF shunting. Initial therapy is generally with amphotericin preparations, often with 5-flucytosine, with later conversion to fluconazole for maintenance. Note that *Cryptococcus* sp. is resistant to the echinocandins.

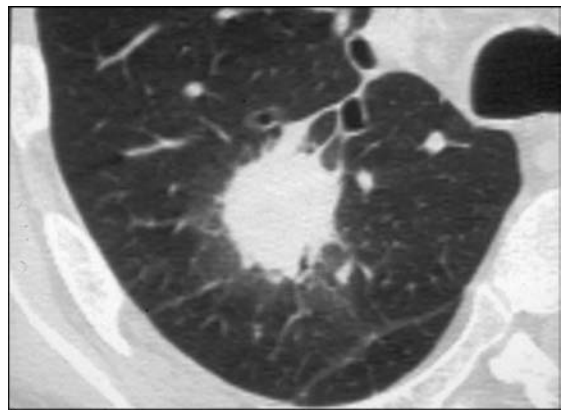

Figure 4.3 Kidney transplant recipient with cough and fever. Pulmonary nodule seen on chest CT scan read as "Likely *Aspergillus*" by radiologist. Biopsy demonstrated *Nocardia asteroides*.

Mold infections

Mold infections often follow environmental (or nosocomial) exposures, beginning with colonization of the airways or sinuses, and followed by invasive infection. *Aspergillus* sp. is particularly common after lung transplantation. Pulmonary nodules, often with associated infiltrates, cavitation, and the "halo sign," are often hallmarks of fungal infection (Figures 4.2 and 4.3). Involvement of the sinuses, orbits, brain, and other sites may also occur. Mucor and rhizopus infection (members of the Zygomycetes) are less common but may be increasing with widespread use of voriconazole (to which they are resistant.) Non-aspergillus molds such as *Scedosporium* and *Paecilomyces* spp. are often resistant to multiple antifungal agents and are increasing in frequency. Culture and species identification with susceptibility testing are crucial to management of these life-threatening infections.

Endemic mycoses

Histoplasmosis, blastomycosis, and coccidioidomycosis are caused by dimorphic or "geographic" fungi. These organisms are yeasts at body temperature and molds at room temperature. They occur in geographically restricted areas, e.g. histoplasmosis in the midwest and coccidioidomycosis in the southwestern USA. Pretransplant screening for coccidioidomycosis

is frequently performed by centers in the southwest USA. Past histoplasmosis is manifested by calcified lymph nodes and splenic calcifications. Disseminated infection may present with fever and pancytopenia, or gastrointestinal or splenic involvement. Fungal serologies may be falsely negative, and cultures or histology (e.g., of bone marrow or lung tissues) may be necessary for diagnosis. The histoplasma urinary antigen may be helpful. These fungi are susceptible to azole therapy and long-term therapy is required after transplantation.

Pneumocystis

Pneumocystis jiroveci causes a diffuse pneumonia (PCP as formerly known as *Pneumocystis carinii*) that presents with progressive dyspnea and hypoxemia out of proportion to physical findings. *Pneumocystis* sp. requires universal prophylaxis for at least the first 6–12 months after transplantation. In high-risk patients, such as lung transplant recipients or those with CMV or other chronic viral infections, lifelong prophylaxis may be indicated. Trimethoprim–sulfamethoxazole (TMP-SMX, either daily or three times weekly) is the drug of choice for prophylaxis. TMP-SMX also provides some prophylaxis against *Nocardia*, *Listeria*, and *Toxoplasma* spp. pulmonary, gastrointestinal, and urinary tract infections. Sulfa-allergic patients may receive atovaquone, aerosolized pentamidine, or dapsone for PCP prophylaxis. Breakthrough infections with PCP may be seen with inhaled pentamidine (upper lobes). Glucose-6-phosphate dehydrogenase (G6PD) screening should be obtained before using dapsone. TMP-SMX should be the drug of choice unless significant allergy or intolerance can be demonstrated.

Prevention of fungal infections

Environmental exposures are critical to the pathogenesis of fungal infections. Hospital or domiciliary construction causes aerosolization of fungal spores. Inpatients should wear masks when out of a filtered environment, especially when construction is occurring. Fungal colonization is more likely in patients with outdoor occupations or hobbies. Patients should be advised to avoid these activities for at least the first 6–12 months and should consult with their transplant clinician before resuming them.

Fungal prophylaxis or pre-emptive therapy remains controversial, but should be determined by the epidemiology of the geographic region and center, and based on any unique epidemiologic exposures. High-risk populations such as lung, pancreas, and some liver recipients are candidates for prophylaxis. Fluconazole and liposomal amphotericin have been used for liver or pancreas recipients; inhaled amphotericin or liposomal amphotericin, itraconazole, and voriconazole are used for lung transplant recipients, but practices vary. Interactions between azoles and calcineurin inhibitors or sirolimus must be carefully monitored. Most transplant recipients receive oral nystatin or clotrimazole in the first month for prevention of oral candidiasis.

Parasitic infections

Toxoplasma gondii is a protozoan parasite that is transmitted by eating undercooked meat or by contact with cat feces, and can reactivate in the transplant recipient. The organism encysts in skeletal and cardiac muscle and may be transmitted from a *Toxoplasma*-seropositive donor to a seronegative recipient of cardiac or other organs. Toxoplasmosis manifests as focal brain lesions, encephalitis, or pulmonary infiltrates. TMP-SMX (notably double strength daily) appears to prevent reactivation. However, some experts recommend pyrimethamine/clindamycin/leukovorin or atovaquone for early prophylaxis in D+/R– heart transplant recipients.

Trypanosoma cruzi causes Chagas' disease in endemic areas of Latin America. After an early febrile illness, cardiomyopathy, megacolon, or megaesophagus may occur years later. Donor-derived transmission has occurred, notably after heart transplantation. Screening should be considered for patients from endemic areas.

Strongyloides sp. is endemic in much of Asia, the tropics and southeastern USA. Infectious larvae penetrate skin and migrate to the intestine, where an autoinfection cycle may result in persistent infection for decades. When immunosuppression is initiated, disseminated infection may occur with a fatal outcome over 30 years after initial exposures. The parasite migrates widely and carries along enteric bacteria, resulting in diffuse pulmonary infiltrates, Gram-negative bacteremia, and meningitis. Pretransplant

strongyloides serology (and therapy with ivermectin if positive) is recommended for any patient who has lived or traveled in an endemic area.

Case

A patient originally from southeast Asia underwent a renal transplant. Two months later, he presented with *E. coli* bacteremia and sepsis and progressed to respiratory and multiorgan failure. Strongyloides serology was positive. Despite therapy with ivermectin and broad-spectrum antibiotics, he died after a lengthy course.

Immunizations pre- and post-transplant

Vaccine-preventable diseases may cause severe complications in the transplant recipient (see Table 4.6). Vaccine efficacy is often suboptimal post-transplantation, and live vaccines are contraindicated. Anecdotal reports (e.g., regarding tetanus immunization post-transplantation) have raised concerns about triggering rejection, but larger studies have not documented increased rates of rejection in immunized transplant recipients. Live vaccines that are contraindicated in transplant recipients include varicella, measles–mumps–rubella (MMR), oral polio, oral typhoid, and smallpox vaccine (see Table 4.6). Inactivated polio and typhoid vaccines are acceptable. Household contacts of transplant recipients can receive MMR and varicella vaccine. Smallpox vaccine (vaccinia) can be transmitted by direct contact with the inoculation site and may cause severe vaccinia infection in the immunocompromised host. Covering the site with a bandage for 3 weeks after immunization and avoidance of direct contact can help to prevent transmission. The pretransplant evaluation should prompt re-evaluation of the candidate's vaccine status. Ideally vaccines should be administered before the onset of end-stage organ disease. If the patient is seronegative for hepatitis B, a three-dose HBV series should be given, as the patient may be offered a transplant from a HBcAb-positive donor. An enhanced-potency or accelerated regimen may be considered. Adults should receive pneumococcal vaccine and a tetanus–diphtheria booster pretransplant if not given in the last 5 years (see AST ID Guidelines for pediatric recommendations). The varicella-seronegative patient should receive varicella vaccine, but not if transplantation is anticipated within the next 3 weeks. Post-transplantation, yearly influenza immunization (both seasonal and novel H1N1 injected vaccines) and updating of the pneumococcal immunization every 5 years (or more frequently in high-risk cases) is recommended.

Further reading

American Society of Transplantation Infectious Disease Community of Practice. Guidelines for the prevention and management of infectious complications in solid organ transplantation. *Am J Transplant* 2009;**4**(suppl 9): 5–166.

Asberg A, Humar A, Rollag H, et al. Valganciclovir is non-inferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007;**7**:2106–13.

Avery RK, Michaels M. Update on immunization in solid organ transplant recipients: what clinicians need to know. *Am J Transplant* 2008;**8**:9–14.

Doucette K, Fishman JA. Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. *Clin Infect Dis* 2004;**38**:1428–39.

Falagas ME, Snydman DR, Griffith J, Werner BG. Exposure to cytomegalovirus from the donated organ is a risk factor for bacteremia in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG Study Group. *Clin Infect Dis* 1996;**23**:468–74.

Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998;**338**:1741–51.

Fishman JA, Doran MT, Volpicelli SA, Cosimi AB, Flood JG, Rubin RH. Dosing of intravenous ganciclovir for the prophylaxis and treatment of cytomegalovirus infection in solid organ transplant recipients. *Transplantation* 2000; **69**:389–93.

Fishman JA. Infections in solid organ transplantation. *N Engl J Med* 2007;**357**:2601–14.

Fishman, JA. Transplantation for patients infected with human immunodeficiency virus: No longer experimental, but not yet routine. *J Infect Dis* 2003;**188**:1405–11.

Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. *Infectious Dis Clin North Am* 1995;**9**:1045–74.

Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med* 2005;**143**: 870–80.

Kotton CN, Ryan ET, Fishman JA. Prevention of infection in adult travelers after solid organ transplantation. *Am J Transplant* 2005;**5**:8–14.

Limaye AP, Corey L, Koelle DM, Davis CL, Boeckh M. Emergence of ganciclovir-resistant cytomegalovirus disease

among recipients of solid-organ transplants. *Lancet* 2000;**356**:645–9.

Lloveras J, Peterson PK, Simmons RL, et al. Mycobacterial infections in renal transplant recipients: seven cases and a review of the literature. *Arch Intern Med* 1982;**142**: 888–892.

Paya CV. Fungal infections in solid organ transplantation. *Clin Infect Dis* 1993;**16**:677.

Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. *ASTS/ASTP EBV-PTLD Task Force Transplantation* 1999;**68**:1517–25.

Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004;**4**:611–20.

Preiksaitis JK, Brennan DC, Fishman JA, Allen U. Canadian Society of Transplantation workshop on cytomegalovirus management in solid organ transplantation: final report. *Am J Transplant* 2005;**5**:218–27.

Razonable RR, Rivero A, Rodriguez A, et al. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *J Infectious Dis* 2001;**184**:1461–4.

Reinke P, Fietze E, Ode-Hakim S, et al. Late-acute renal allograft rejection and symptomless cytomegalovirus infection. *Lancet* 1994;**344**:1737–8.

Rodriguez M, Fishman JA. Prevention of infection due to *Pneumocystis* in HIV-negative patients. *Clin Micro Rev* 2004;**17**:770–82.

Scharpe J, Evenepoel P. Maes B, et al. Influenza vaccination is efficacious and safe in renal transplant patients. *Am J Transplant* 2007;**7**:1–6.

Sia IG, Wilson JA, Groettum CM, Espy MJ, Smith TF, Paya CV. Cytomegalovirus (CMV) DNA load predicts relapsing CMV infection after solid organ transplantation. *J Infectious Dis* 2000;**181**:717–20.

Singh N, Lortholary O, Alexander BD, et al. Antifungal management practices and evolution of infection in organ transplant recipients with *Cryptococcus neoformans* infection. *Transplantation* 2005;**80**:1033–9.

Wilck M, Fishman JA. The challenges of infection in transplantation: donor-derived infections. *Curr Opin Organ Transplant* 2005;**10**:301–6.