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Life-Threatening Infection in Transplant Recipients

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KEYWORDS

• Transplant infection • Critical care • Immunosuppression • Opportunistic infection
• Microbiological diagnosis

KEY POINTS

- Transplant patients represent a heterogeneous and rapidly growing patient group requiring a high index of suspicion for infection.
- Infection is a major posttransplant cause of morbidity and mortality, and new threats continually emerge.
- Individualized assessments of net state of immunosuppression and infection risk are important.
- Aggressive pursuit of an early microbiological diagnosis is crucial; invasive procedures should be used if necessary.
- In the setting of life-threatening infection, reduction or cessation of immunosuppressive therapy whenever possible is an important adjunct to therapy.

INTRODUCTION

Transplant recipients constitute an increasingly diverse and complex patient cohort. They comprise a heterogeneous patient group undergoing solid organ transplantation (SOT), hematopoietic stem cell transplantation (HSCT), or pancreatic islet cell transplantation, and now also include the emerging group of individuals undergoing vascularized composite allotransplantation, such as limb transplants. Infection remains a major cause of morbidity and mortality in transplant recipients; for example, approximately 17% to 20% of the mortality following allogeneic HSCT can be attributed to infection.[1–3]

In SOT where immunosuppressants are prescribed indefinitely, transplant physicians and their patients perpetually negotiate the delicate balance between the risk of graft rejection and infection. Advances in techniques and in modern immunosuppression have improved graft survival but continually unveil new infection challenges

Disclosures: A. Humar has received grant support from Roche and consulting fees from Astellas.
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Crit Care Clin 29 (2013) 953–973
http://dx.doi.org/10.1016/j.ccc.2013.06.012 criticalcare.theclinics.com
0749-0704/13/$ – see front matter

for the patient.[4–6] The pharmacology of immunosuppression has evolved dramatically in recent years with a plethora of agents now available for physicians to use (**Box 1**).[7] Specific agents vary greatly in their mode, intensity, and duration of immunosuppression, adding yet another layer of complexity to the management and prevention of infectious morbidity and mortality in transplant recipients.[8]

The risk of infection in transplant recipients is a dynamic process and numerous influencing factors must be considered during the evaluation of patients (**Box 2**). The net state of immunosuppression is a central concept in transplantation medicine and represents a key determinant of infectious risk.[1,9] The net state is a measure of an individual's unique susceptibility to infection and incorporates assessment of several important contributing factors

- Pretransplant diagnosis or treatment (eg, myeloablative conditioning before HSCT)
- Induction therapy used at time of transplantation
- Nature of organ or stem cell transplant received (eg, lung vs liver organ transplant or umbilical cord blood, T-cell-depleted stem cell transplants)
- Dose, duration, and choice of maintenance immunosuppression
- Comorbidities (eg, viral coinfection [hepatitis C virus (HCV), cytomegalovirus (CMV)], malnutrition, end-organ failure [cirrhosis, chronic kidney disease])
- Breaches of the mucocutaneous barrier: indwelling devices, mucositis

The time after transplant is also of key importance (**Fig. 1**, **Table 1**). It directly influences the potential pathogens from which an individual patient is at risk.[1] Following periods of intensification of immunosuppression (eg, due to graft rejection or flare of Graft-versus-host disease [GVHD]) the patient's infection risk is adjusted to reflect earlier time points again after transplantation. In the absence of chronic GVHD requiring ongoing immunosuppression in HSCT recipients, immune restitution can in general be considered complete at 2 years after stem cell transplant.[3]

The authors' learning objective is to review significant posttransplant infections that can necessitate critical care support. For ease of description this discussion is divided into infections presenting early after transplantation and those occurring later after transplantation. A more detailed discussion of specific pathogens will then follow.

Early infections are classified here as

- SOT: those encountered between the transplant procedure and 4 weeks after transplantation
- HSCT: infection occurring in the preengraftment phase

Box 1
Immunosuppressant therapies and mechanism of action

Corticosteroids—multiple anti-inflammatory effects

Anti-proliferative agents: mycophenolate mofetil—inhibit nucleotide synthesis and prevent T-cell and B-cell proliferation

Calcineurin inhibitors: cyclosporine, tacrolimus—inhibits T-cell activation

mTor inhibitors: sirolimus—inhibits T-cell activation and proliferation

Monoclonal antibodies: basiliximab (IL-2 receptor antagonist), alemtuzumab (anti-CD52: prolonged T-cell, B-cell depletion), belatacept (binds CD80/86 to prevent T-cell costimulatory signal)

Antilymphocyte antibodies: anti-thymocyte globulin—prolonged T-cell depletion

Box 2
Infection risk assessment after transplantation

- Net state of immunosuppression
- Time after transplantation
- Type of transplant (highest risk in SOT is lung transplant; in HSCT is T-cell depleted grafts or cord blood stem cell transplants)
- HLA mismatch, episodes of graft rejection
- Prior antimicrobial exposure: prophylactic/therapeutic
- Prior colonization with drug resistant organisms
- Prolonged hospitalization
- Ongoing neutropenia, lymphopenia, or hypogammaglobulinemia

Infectious entities unique to transplant recipients, and emerging pathogens of importance, are emphasized with the understanding that many more frequently observed infections (dealt with in other articles) are equally applicable to this cohort of patients.

GENERAL PRINCIPLES OF ASSESSMENT

Transplant recipients are frequent users of critical care services, and the intensivist forms an integral part of posttransplant care pathways. Following SOT, many patients routinely receive their initial period of postoperative care in the critical care setting. In later posttransplant periods these patients can require critical care support for the management of infections manifesting as severe septic shock or in the setting of severe compromise of a vital organ function (eg, pneumonia) or disease affecting the central nervous system (CNS).

Recognition of infection in transplant recipients is notoriously difficult and maintaining a high index of suspicion is of paramount importance. The presentation of infection is frequently altered due to impaired innate and adaptive immune responses. The absence of fever does not preclude the possibility of serious infection and localizing signs may be absent or only identifiable late in the disease process. A multidisciplinary approach is essential to achieve optimal outcomes for patients. This approach involves transplant physicians, transplant surgeons, critical care clinicians, clinical pharmacists, and allied health specialists all working together.

At the core of successful diagnosis and management is a thorough assessment of infectious risk, and a detailed history and physical examination inclusive of cutaneous and ophthalmologic examinations, which can frequently provide subtle but vital diagnostic clues.

Microbiological diagnosis is crucial in this patient group. In the context of extensive differential diagnoses, the value of early and specific diagnostics with the use of invasive procedures if necessary (bronchoscopy, tissue biopsy, or aspiration of collections) to obtain specimens cannot be overemphasized (**Box 3**). After transplantation, serologic techniques are of limited use because transplant recipients may not mount timely serologic responses. Antigen detection or molecular nucleic acid detection assays are preferred. Adoption of newer microbiological techniques for pathogen identification carries the potential to improve the ability to achieve a definitive diagnosis, greatly enabling the prompt commencement of specific antimicrobials.[10,11]

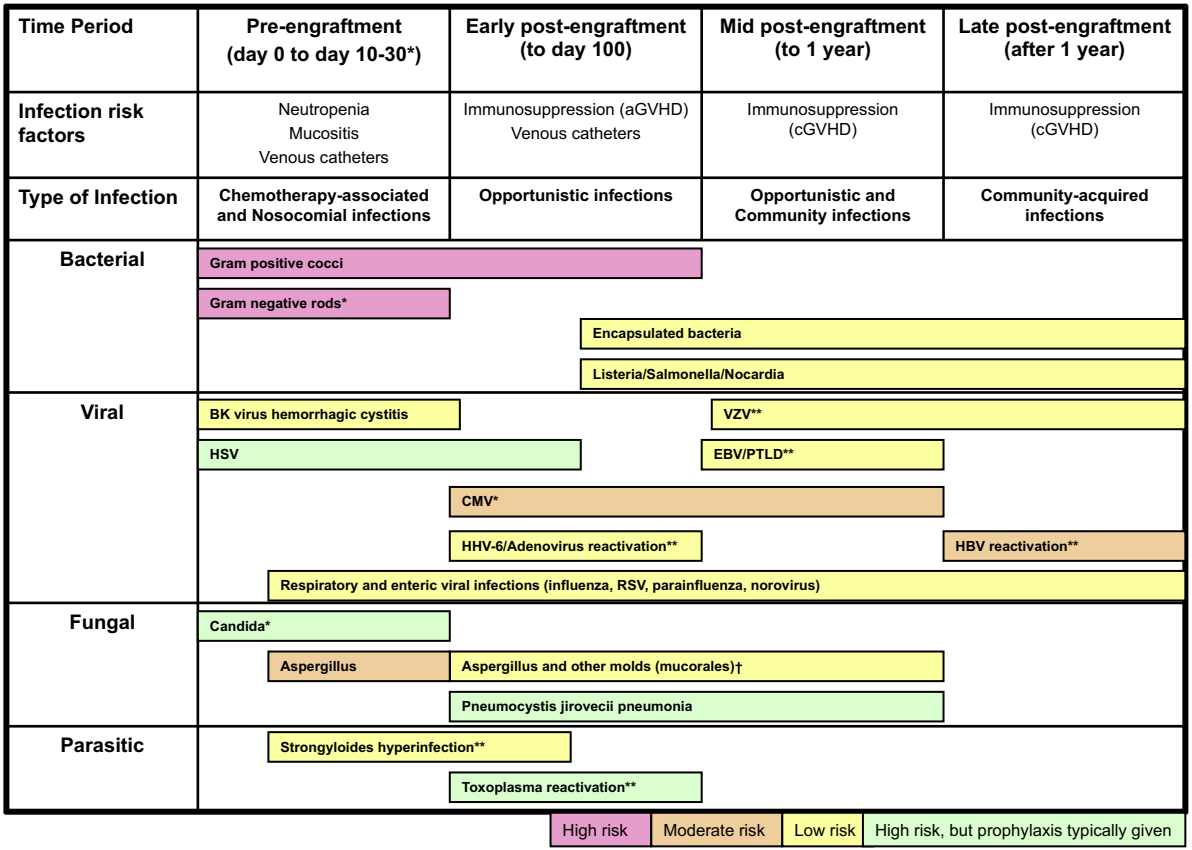

Fig. 1. Timeline of infections after hematopoietic stem cell transplant. *Some centers mitigate this risk with prophylaxis. **In previously exposed recipients. †High risk in those with severe GVHD. §Timeline described is primarily for those undergoing myeloablative conditioning. (*From* Marty FM, Baden LR. Infection in the hematopoetic stem cell transplant recipient. In: Soiffer RJ, editor. Hematopoetic stem cell transplantation. Totowa (NJ): Humana Press, 2008. p. 423; with kind permission from Springer Science and Business Media.)

Table 1
Timeline of infections after organ transplant

Time Period	0–1 mo Posttransplant	1–6 mo Posttransplant	>6 mo Posttransplant
Type of infection	Nosocomial infections: pneumonia, catheter-related, UTI Postsurgical infections: wound, anastomotic leaks, abscesses Donor-derived infection	Opportunistic infection Reactivation of recipient or donor-latent infections (prophylaxis may shift further)	Community-acquired infections In the absence of prophylaxis: reactivation of latent infections during intense immunosuppression for acute graft rejection
Bacterial	*C difficile* colitis Antimicrobial-resistant bacteria (MRSA, VRE, ESBL, multi-drug resistant (MDR) gram-negative rods) Postsurgical infections (infected biliomas in liver transplant, pneumonia in lung transplant, UTI in renal transplant)	Listeria, Nocardia (if no TMP/sulfamethoxazole) *M. tuberculosis*, *Legionella*	Ongoing risk for *Listeria, Nocardia, M tuberculosis, Legionella* if ongoing intense immunosuppression Graft-related infections (cholangitis in liver, pneumonia in lung, UTI in kidney) Community-acquired pneumonia pathogens
Viral	In the absence of anti-herpes virus prophylaxis: HSV Donor-derived: lymphocytic choriomeningitis virus, rhabdovirus, West Nile virus, HIV	BK nephropathy (kidney), HCV reactivation (liver), adenovirus, respiratory viruses CMV, EBV, HSV, VZV (after discontinuation of prophylaxis)	Late-onset CMV (postprophylaxis), EBV-related PTLD, recurrent HSV, VZV, HCV progression, JC polyomavirus Respiratory viruses, enteric viruses, West Nile virus
Fungal	*Candida* spp Early Aspergillus only in some settings	*Cryptococcus, Aspergillus*, atypical molds, *Zygomycetes* species *Pneumocystis* only if no prophylaxis	During intense immunosuppression in the absence of antifungal prophylaxis: *Aspergillus*, atypical molds, *Zygomycetes* species Geographically restricted endemic fungi
Parasitic	Uncommon	*Toxoplasma, Strongyloides, Trypanosoma, Leishmania*	Ongoing risk if intense immunosuppression

From Deepali K, Humar A, editors. The AST handbook of transplant infections. Hoboken (NJ): Wiley Blackwell; p. 3; with permission.

Box 3
Initial infectious diagnostic evaluation in transplant recipients

Multiple blood cultures (from periphery and central vascular catheters if present)

Urine culture

Respiratory specimen for culture

Radiological imaging: chest radiograph, CT

Specific diagnostics (see later) according to site of infection/potential pathogens/ epidemiologic risk (eg, CMV PCR, CSF sampling, bronchoalveolar lavage)

Detailed radiological examinations using computed tomography (CT) scan or magnetic resonance imaging (MRI) allow the early identification of occult sites of infection.

However, in most instances, following the collection of initial specimens for culture, immediate institution of empiric broad antimicrobial coverage targeting the likely pathogens is imperative.

Noninfectious entities can also precipitate illness requiring critical care support in transplant recipients and may mimic infection; these should always be borne in mind. Transplant recipients are susceptible to episodes of graft rejection, GVHD flares, or even recurrence of their primary disease. In addition, adverse effects arising from drug toxicity or drug-drug interactions, which can resemble infectious entities, may be observed (eg, Sirolimus-induced pneumonitis).[12,13]

Effective management of infection after transplantation often necessitates a reduction in immunosuppression if possible. This management alters the net state of immunosuppression in favor of enabling a more robust host immune response. Adjuvant immunotherapy using immunoglobulin is used for certain infections.[14] Additional therapeutic concerns relate to drug interactions between antimicrobials and immunosuppressant drugs, and appropriate dosing and delivery in the critically ill patient with vital organ dysfunction.[13] Surgical intervention may be required to aid diagnosis or to effect definitive management.

Early Posttransplantation Period

In the early period posttransplantation, bacterial infections predominate. Frequent issues arising relate to common nosocomial infectious complications, such as[2,15,16]

- Bloodstream infection (BSI), catheter-associated BSI[17]
- Health care/ventilator-associated pneumonia
- Urinary tract infections (UTI)
- Surgical site infections
- *Clostridium difficile*-associated diarrhea

The risk of these infections relates to the technical difficulty of the transplant procedure, as well as the pretransplant status of the recipient. The usual nosocomial pathogens prevail, such as *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, enterobacteriaceae, and *Pseudomonas aeruginosa*. As a consequence of significant health care exposure antimicrobial-resistant pathogens (methicillin-resistant *S aureus* [MRSA], vancomycin-resistant *Enterococcus* [VRE], extended spectrum β-lactamase [ESBL] -producing gram-negative organisms) are encountered with increased frequency in transplant recipients.[18–25] In addition, antimicrobial prophylaxis and prior treatment episodes can markedly alter an individual's commensal flora. Thus a heightened awareness of organisms less frequently encountered is

required and in certain circumstances empiric therapy should take these organisms into consideration (eg. *Stenotrophomonas maltophila, Acinetobacter baumannii* complex) given the mortality associated with delayed therapy.[17,26,27]

Candida infections and candidemia are frequently encountered in the critical care setting. The prevalence of non-*albicans Candida* species continues to increase and in transplant recipients this shift can be further promoted by the use of antifungal prophylaxis following HSCT or solid-organ transplantation.[28]

C difficile

Transplant recipients have an increased incidence of infection because of *C difficile* and experience more severe disease. The highest incidence is in the first 3 months after transplant. Relapsing disease is common and prolonged courses of therapy are often required.[29,30]

Specific to SOT are the risks of donor-derived infection and infections originating within the operative field.

Donor-derived infection A broad range of potential infecting pathogens can be transmitted by organ transplantation.[31] These infecting pathogens include the following:

- Known latent infections (eg, CMV, Epstein-Barr virus [EBV])
- Unknown latent infections (eg, tuberculosis, endemic mycoses)
- Infections that are not manifest or detected in the donor at the time of transplantation (eg, bloodstream infections, viral infections such as West Nile virus,[32] lymphocytic choriomeningitis virus, human immunodeficiency virus [HIV], HCV).[33,34]

Unexplained fever early after transplant with altered mental status or signs of unexplained multiorgan failure despite thorough investigations raises the possibility of donor-derived infection.[35] Open communication with the relevant organ procurement organizations is vital when such situations arise.

Operative field infections Early posttransplant residual fluid collections or hematomas in conjunction with devitalized tissues or leaking anastomoses can provide the ideal conditions for the establishment of deep-seated infection. Vascular complications such as thrombosis of vessels may also occur, leading to graft ischemia, dysfunction, and necrosis. Early radiological diagnosis and intervention are critical and the approach to diagnosis and management often necessitates surgical intervention for microbiological diagnosis and to perform effective debridement.

ISSUES SPECIFIC TO CERTAIN TRANSPLANT TYPES

Cardiothoracic Recipients

Lung transplant recipients experience the highest frequency of infections among SOT recipients and infection incidence is double that of heart transplant recipients.[36,37] Contributory factors include

- Donor lung colonization[38]
- Extended periods of intubation
- Disruption of lymphatic drainage
- Reduced cough reflex and ciliary function
- More intensive immunosuppression

Particular attention is paid to the bronchial anastomoses, which can be susceptible to ischemia, breakdown, and infection. Mediastinitis and pleural-based disease are prevalent in cardiothoracic transplant recipients and early imaging with CT is indicated

when clinical concern exists.[39] Occasionally culture-negative surgical site infections may be attributable to unusual pathogens such as *Mycoplasma hominis.*[40]

Cystic fibrosis patients undergoing lung transplantation deserve particular mention.[41] They often come to transplant colonized with resistant and fastidious organisms; 52% to 75% are colonized with multi-drug-resistant *Pseudomonas*, and 6% to 9% are colonized with *Burkholderia* spp.[42–44] These patients require individualized antimicrobial prophylactic regimens but breakthrough infection can still occur. This breakthrough infection can manifest as sepsis, empyema, lung abscess, or central venous catheter—associated BSI early or late after transplant. Close surveillance and early aggressive therapy are essential. Antimicrobial therapy should be optimized based on susceptibility testing. Source control, entailing catheter removal or drainage of sites of infection, should be pursued.

Abdominal Organ Transplantation: Liver, Pancreas, Kidney, Intestinal

In critical care settings, early posttransplantation nosocomial infections again prevail.[16] Gram-negative bacilli, enterococci, and anaerobic organisms represent the predominant pathogens. Infections related to technical complications are common. These infections may be due to vascular or nonvascular anastomotic problems and a thorough understanding of the transplanted organ anatomy is important. For example, in liver transplant recipients the biliary anastomosis may leak or stricture. Biliary leaks or bilomas represent common sites for the initiation of infection. Thrombosis of the hepatic artery is uncommon but may lead to devastating complications, including hepatic abscesses, necrosis, and sepsis. Early imaging and diagnosis are essential in this setting.

Liver, pancreas, and intestinal recipients are at particular risk for fungal infection most often caused by *Candida* species.[28] Close surveillance is required and antifungal prophylaxis is recommended for patients at high risk (intestinal recipient, reoperation, retransplantation, renal failure, massive transfusion, *Candida* colonization).[45,46]

HSCT Recipients

During the pre-engraftment phase HSCT recipients most commonly require critical care support due to sepsis or pneumonia.[15]

BSI

Severe mucositis predisposes to the establishment of BSI by skin, oral, or gastrointestinal (GI) tract flora. Catheter-associated BSI is also common. The spectrum of BSI pathogens has altered over time. Following the introduction of fluroquinolone prophylaxis, the incidence of GNB infection declined but was replaced with increasing incidence of gram-positive organisms.[47,48] The spectrum reflects the prevailing organisms present within an institution but common to all is a rising incidence of drug-resistant organisms that carry an increased risk of mortality (eg, VRE, ESBL-producing enterobacteriaceae).[22] Akin to SOT recipients, due consideration should be given to the possibility of unusual bacterial pathogens.

Candida BSI is also increasingly due to non-albicans species reflecting the use of antifungal prophylaxis. Candidemia in transplant recipients should prompt a search for end-organ sites of infection, such as endocarditis, endophthalmitis, renal abscesses, or hepatosplenic candidiasis, depending on the clinical setting.[28]

Pneumonia

Severe pneumonia occurring pre-engraftment can precipitate the requirement for critical care support. Nosocomial organisms or respiratory viruses cause most pneumonias in this setting; however, these patients are also particularly susceptible to invasive

fungal infections (IFI).[49] Prolonged periods of neutropenia pre-HSCT contribute to a substantially increased risk of IFI early post-HSCT. *Aspergillus* is the most common pathogen encountered with an overall incidence of 5% to 30% in allogeneic HSCT recipients.[50] Other molds, namely *Fusarium*, Zygomycetes, and *Scedosporium* spp, are emerging as important causes of IFI in HSCT recipients.[28] All can manifest with pulmonary and/or disseminated extrapulmonary disease (see more detailed discussion later).

The diverse approaches required to manage pneumonia appropriately due to bacterial, viral, or fungal pathogens in this setting emphasize the importance of early microbiological diagnosis using invasive procedures if necessary.

Typhlitis/neutropenic enterocolitis

Typhlitis occurs in approximately 5% of patients with hematologic malignancies.[51–53] Mucosal injury and profound neutropenia allow secondary bowel wall infection and transmural inflammation. The cecum is most often involved and patients present with right lower quadrant pain or peritoneal signs. Progression to septicemia and/or bowel perforation can occur. Typhlitis is a clinical diagnosis supplemented by CT to confirm and establish the extent of disease or the presence of perforation. Conservative management is the mainstay of therapy with bowel rest, total parenteral nutrition, and broad spectrum antimicrobials to cover gut flora (ie, gram-positive, gram-negative, anaerobic organisms, and fungi while awaiting neutrophil recovery).[53] Surgery is recommended only in the case of complications or where conservative management has failed.

LATE INFECTIOUS COMPLICATIONS POSTTRANSPLANTATION

Late post transplantation, infections which are observed in the early posttransplant period continue to be encountered, but opportunistic pathogens and community-acquired infections tend to dominate.[1,9] Again, the intensity of ongoing immunosuppression dictates the breadth of pathogens an individual is susceptible to. To maintain relevance to critical care clinicians, common and emerging infection syndromes unique to transplant recipients are discussed and the approach to diagnosis and initial management is reviewed.

Common community infections, which can require critical care support, such as invasive pneumococcal or staphylococcal disease, urosepsis, meningococcal disease, and influenza, have been reviewed elsewhere. Transplant recipients can present at more advanced stages of illness but the management is broadly in keeping with that in immunocompetent individuals. Decisions to adjust immunosuppression or use adjunctive immunoglobulin therapy are based on the patient's individual clinical circumstances.

Pneumonia

Pulmonary infection is the most common form of documented invasive infection observed in transplant recipients. It will frequently cause sufficient compromise in respiratory function to require critical care support. The differential diagnosis in transplant recipients is very broad (**Box 4**) and definitive diagnosis is crucial to effective therapy and resolution.

Chest radiograph may often underestimate the true extent of disease and CT thorax can provide further information regarding the extent and pattern of pulmonary involvement, such as the presence of cavitation or nodular infiltrates. Routine diagnostic evaluation with blood cultures remains important but specific tests for opportunistic

Box 4
Differential diagnosis of pneumonia in transplant recipients

Bacterial:

Community-acquired pathogens: *S pneumoniae, H influenzae, M catarrhalis, S aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae*

Nosocomial: gram-negative bacilli (*E coli, P aeruginosa, K pneumoniae*), MRSA

Legionella

Nocardia

Rhodoccus equi

Viral:

Respiratory viruses: influenza, parainfluenza, RSV, human metapneumovirus, adenovirus, coronavirus, entero/rhinovirus

CMV, Herpes simplex virus (HSV), Varicella-zoster virus (VZV)

Mycobacteria:

Tuberculosis

Nontuberculous mycobacteria: *Mycobacterium avium* complex (MAC), *M abscessus* (CF patients)

Fungal:

Invasive molds: *Aspergillus, Zygomycetes, Fusarium, Scedosporium*

P jirovecii pneumonia (PJP/PCP)

Cryptococcus (neoformans, gattii)

Endemic mycoses: histoplasmosis, coccidiomycosis, blastomycosis

Parasitic:

Strongyloides hyperinfection syndrome

Toxoplasmosis

pathogens are equally important (eg, plasma CMV viral load estimation by polymerase chain reaction [PCR], serum galactomannan).

Bronchoalveolar lavage (BAL) yields representative specimens of an adequate quality more reliably than sputum collection. Performing a bronchoscopy and BAL should be considered early with specimens processed for the potential bacterial, mycobacterial, fungal, and viral pathogens (see specific pathogens). Clinicians should also maintain a low threshold for performing a biopsy of involved lung tissue for histology and culture.

Central Nervous System Infection

Infection of the CNS in transplant recipients can vary from indolent presentations with chronic low-grade headache, to a more fulminant meningoencephalitic presentation requiring admission to critical care. The CNS may be the only site of infection (isolated intracerebral abscess) or it may be involved as part of a disseminated infectious process. In transplant recipients the differential diagnoses for such presentations are diverse and again cover the spectrum from common community acquired to opportunistic pathogens (**Box 5**).

Box 5
Differential diagnosis of CNS infection in transplant recipients

Intracerebral abscess/space occupying lesion:

Bacterial: embolic or contiguous disease from local site

Nocardia; Listeria monocytogenes

Fungal: *Aspergillus*; zygomycetes; *Cryptococcus*

EBV associated posttransplant lymphoproliferative disorder (PTLD)

Tuberculosis

Toxoplasmosis

Meningoencephalitis:

Bacterial: *S pneumoniae; Neisseria meningitides; Listeria*

Viral: CMV; EBV; HSV; VZV; HHV6; Enterovirus; JC virus

Fungal: Cryptococcus, Coccidioides, Histoplasma capsulatum

Tuberculosis

Treponema pallidum; Borrelia burgdorferi

MRI is the neuroimaging modality of choice providing better resolution of the brain parenchyma and improved diagnostic specificity.[54] Lumbar puncture should be performed if safe, and cerebrospinal fluid (CSF) should be processed for specific pathogen testing (eg, viral PCR, cryptococcal antigen; see specific pathogens).

Enteritis/Colitis

Occasionally severe enterocolitis may require admission to critical care due to cardiovascular compromise or as a consequence of perforation/bleeding. In transplant recipients the predominant infectious etiologies to consider are

- *C difficile*
- CMV, EBV (posttransplant lymphoproliferative disorder [PTLD])
- Norovirus, rotavirus: both can cause protracted diarrheal illnesses
- *Cryptosporidium, isospora, Giardia lamblia*
- *Strongyloides stercoralis* (hyperinfection syndrome)

Specific diagnostic tests include stool specimens for culture, ova/parasite examination, and *C difficile* toxin. Enteric virus PCR on stool samples can be performed if available often with improved sensitivity compared with electron microscopy.[55] Colonoscopy and tissue biopsy may be required to diagnose CMV definitively because in the setting of CMV colitis, CMV may not be detected in plasma by PCR.

SPECIFIC PATHOGENS

Following is a discussion of selected pathogens that are particularly common causes of life-threatening or severe illness in transplant recipients.

CMV

CMV is one of the most prevalent opportunistic pathogens posttransplant. Before the development of sensitive diagnostic tests and the advent of prophylactic/preemptive strategies, CMV reactivation rates of 70% to 80% were observed with significant attributable morbidity and mortality.[56,57] Currently, with the widespread use of

prophylaxis and preemptive prevention strategies, mortality due to CMV has declined substantially. Despite these advances, CMV remains an important pathogen after transplantation. Seronegative SOT recipients of CMV-seropositive organs are the group at highest risk for severe CMV disease.[58] In HSCT, seropositive recipients receiving stem cells from a seronegative donor represent the highest risk group.[59]

CMV after transplantation can manifest clinically in several ways

- Fever alone
- CMV syndrome: fever with evidence of myelosuppression, arthralgias, myalgias
- Invasive disease: pneumonitis, enterocolitis, encephalitis, hepatitis (retinitis is rare)

CMV is most frequently detected 1 to 4 months after transplant but late-onset disease is being increasingly reported, the natural history being altered by the use of antiviral prophylaxis.[60,61]

Diagnosis

CMV DNA in plasma can be rapidly detected by quantitative PCR. Alternatively, an antigen-detection assay (pp65 antigenemia test) is available. Histology remains the gold standard to prove tissue invasive disease but is often only necessary to diagnose colitis when occasionally CMV DNA can be undetectable in the plasma by PCR.[58] CMV PCR can also be performed on clinical samples from other sites of infection, such as CSF.

Treatment

Severe disease is best treated initially with intravenous ganciclovir 5 mg/kg every 12 hours.[62,63] Initial oral valganciclovir is only an option in patients with mild or no symptoms.[64] The dose of both agents requires adjustment in the setting of renal impairment. Patients often require a reduction in immunosuppression if possible. CMV immunoglobulin (cytogam) may have additive benefit in severe disease and in particular for CMV pneumonitis.[14] Recommended dosing is 100 to 150 mg/kg 3 times per week.[62] Treatment is continued until resolution of viremia.

EBV-associated PTLD

EBV and associated PTLD cause a wide spectrum of clinical conditions ranging from uncomplicated infectious mononucleosis to true malignant disorders.[65] The estimated incidence of PTLD is 3% to 10% in SOT recipients and up to 18% in high-risk HSCT recipients (HLA mismatch, GVHD, T-cell-depleted transplants).[66–68] Attributable mortality approaches 40% to 60%. This entity most often manifests as a nonspecific febrile illness. Approximately 25% of patients have involvement of the GI tract. CNS disease can on occasion lead to a fulminant course and dramatic presentations requiring critical care support.

Diagnosis

Quantitative EBV viral load testing can be performed on whole blood, plasma, and CSF if indicated.[69,70] Radiological assessment/staging requires positron emission tomography -CT scanning and brain MRI. Adequate tissue sampling and histologic staining for morphology and in situ hybridization studies confirm the diagnosis.

Treatment

Many different modalities can be used for treatment.

- Reduction of immunosuppression
- Surgical excision of localized lesions (eg, GI tract masses)

- Ganciclovir/valganciclovir have variable efficacy
- Adoptive immunotherapy
- Anti-CD20 monoclonal antibody (Rituximab)
- Cytotoxic chemotherapy

Respiratory Viruses

Respiratory syncytial virus (RSV), parainfluenza, influenza, human metapneumovirus, adenovirus, entervirus, rhinovirus, coronavirus

These common respiratory viruses are frequently encountered in transplant recipients and attack rates follow the usual seasonal pattern.[71] In immunocompetent individuals most cause only mild symptoms but progression to involvement of the lower respiratory tract and more severe disease occurs with increased frequency in transplant recipients.[72,73] Pediatric patients are at higher risk for both infection and severe disease.[74]

Diagnosis

Specific viruses can be detected by direct fluorescence antibody, culture, or multiplex PCR from nasopharyngeal swabs or BAL specimens.[71]

Treatment

Aside from antiviral therapy for influenza, no consensus exists for the treatment of other respiratory viruses.[75] Early treatment in certain patients (lung transplant recipients, HSCT patients preengraftment) can be used to reduce the risk of lower tract disease and limit severity.[76,77] Treatments reported to demonstrate efficacy are detailed below.

- RSV: aerosolized Ribavirin ± intravenous immunoglobulin (IVIg).[77] Palivizumab (anti-RSV monoclonal antibody) has also provided additive benefit to Ribavirin[78]
- Parainfluenza: aerosolized Ribavirin ± IVIg[79]
- Human metapneumovirus: an emerging respiratory pathogen that has been associated with severe, often fatal disease in HSCT recipients.[80] Aerosolized Ribavirin and IVIg have also been used with some success in case reports[81,82]
- Adenoviridae can cause a wide range of clinical syndromes; self-limited fever, pneumonitis, hepatitis, hemorrhagic colitis.[83,84] Rarely, adenovirus can cause a severe disseminated disease with multi-organ failure. This manifestation occurs more frequently in pediatric recipients and carries a high mortality.[85] Treatment options include cidofovir and ribavirin or the experimental drug CMX001.[86,87]

Aspergillus spp

Aspergillus is the most common cause of IFI in allogeneic HSCT recipients with an incidence of 5% to 30%.[49,50,88] In SOT recipients the incidence is considerably lower, 1% to 15%.[89,90] Mortality attributable to invasive aspergillosis (IA) has varied from 65% to 92% in transplant recipients, although it may be lower in the current era.[90] Risk factors for IA include prolonged neutropenia, lung transplantation, CMV infection, *Aspergillus* colonization, graft rejection/failure, GVHD, and iron overload.

The lungs and sinuses are the most common sites of disease involvement. Patients can present with fever, chest pain, hemoptysis, or dyspnea. Pulmonary disease can involve lung parenchyma only or present as a more diffuse tracheobronchitis. Sinus disease can cause facial pain and seizures, or focal neurologic signs with extensive disease.

Pulmonary radiologic appearances are best appreciated using CT and include nodules with or without cavitation, or patchy segmental areas of consolidation or ground

glass change. Disease outside of the respiratory tract can occur with cutaneous involvement or solitary intracerebral abscesses.

Diagnosis

Sputum culture lacks sensitivity and the isolation of *Aspergillus* alone does not reflect disease. The gold standard for diagnosis is the demonstration of the organism and angio-invasive disease in tissue biopsies (lung or sinus tissue).[90] Fungal stain and culture of such specimens to confirm genus and species remain very important in diagnosis particularly now in the era of prophylaxis using second-generation triazoles (voriconazole, posaconazole), which have altered the spectrum of species encountered.[91,92]

Galactomannan is a constituent of the *Aspergillus* cell wall and is released during hyphal growth. Estimation of galactomannan in serum is widely used but lacks sensitivity. This test appears to perform better in hematological patients than SOT recipients.[93] Estimating galactomannan in BAL demonstrates superior sensitivity,[94] and it can also be performed on CSF specimens but has not been widely standardized. The evolution of molecular assays using PCR should add to the ability to achieve a definitive diagnosis.[95]

Treatment

Voriconazole is now the accepted treatment of choice.[96] A loading dose of 6 mg/kg every 12 hours is administered on day 1 followed by maintenance of 4 mg/kg 12 hourly thereafter. The measurement of trough levels is advised after approximately 1 week of therapy (target range, 1–5.5 μg/mL).[97] Voriconazole interacts significantly with calcineurin inhibitors and thus levels of these agents must also be closely monitored. A minimum of 12 weeks of therapy is advised and duration can be guided by clinico-radiologic resolution and surveillance galactomannan assays.

Again species confirmation is vital to guide therapy because the susceptibility of different species (*Aspergillus terreus, Aspergillus calidoustus*) can vary considerably, and novel antifungal combinations may be required.[98] Surgical intervention is indicated in the context of significant hemoptysis or extensive sinonasal disease.

Other Molds Causing IFI

These pathogens cause disease that mimics IA and represent a considerable emerging threat in the era of posaconazole/voriconazole prophylaxis.[5,28,99] Pathogens of note include zygomycetes, *fusarium*, and *scedosporium*.[100–103]

Pneumocystis Jirovecci Pneumonia/PCP

Effective prophylaxis has dramatically reduced the incidence of *Pneumocystis jirovecci* pneumonia (PJP) in transplant recipients.[104] However, it remains a pathogen of note and is an important diagnostic consideration in a transplant patient presenting acutely with respiratory failure.[105] Classically patients present with subacute fever, cough, and dyspnea. The hallmark of PJP remains profound hypoxia with a relative paucity of clinical findings. Chest radiographs may reveal bihilar infiltrates or pneumothoraces but are often quite unremarkable, and CT thorax is more sensitive for diagnosis.

Diagnosis

Diagnosis is best achieved via the demonstration of the organism in BAL or lung biopsy specimens.[106] Several specific staining methods can be used including monofluorescent antibody stains, gomori-methanamine silver stain, or Giemsa and Wright

stains. The infectious burden is generally less in SOT recipients; thus, the diagnostic sensitivity is lower than the 98% reported in patients with HIV.[106]

Treatment

Trimethoprim (TMP)/sulfamethoxazole remains the treatment of choice. Recommended dosing is 15 to 20 mg/kg/d of the TMP component in 3 to 4 divided doses.[105] Adverse effects are frequent (rash, nausea, renal impairment) and alternatives include clindamycin (600–900 mg 6–8 hourly) and primaquine (15–30 mg daily); or dapsone (100 mg daily) and TMP (15 mg/kg/d in 3 divided doses). As in HIV, adjunctive corticosteroids are an important consideration and are generally recommended in cases with severe hypoxemia (Pa_{O_2} <70 mm Hg).[107] Doses in the region of 40 to 60 mg twice daily for 1 week followed by a taper over 2 weeks are used.

Strongyloides Hyperinfection Syndrome

Strongyloides hyperinfection syndrome is a rare but particularly severe manifestation of latent *Strongyloides* infection primarily reported in SOT recipients.[108–110] Massive dissemination of filariform larvae to the lungs, liver, heart, and CNS occurs. Concomitant gram-negative BSI or bacterial meningitis is recognized. Patients present with a severe systemic illness and mortality is high. Diagnosis is achieved via detection of the larvae in stool, respiratory secretions, or CSF. Treatment is with ivermectin 200 μg/kg/d or albendazole 400 mg twice daily. Extended courses are advised in the setting of hyperinfection in transplant recipients.

SUMMARY

Transplant recipients represent a complex, heterogenous patient population who often require periods of critical care support. Infectious complications precipitate the majority of admissions to critical care post-transplantation, and patients are susceptible to an increasingly diverse array of common and opportunistic infecting pathogens. Clinicians must maintain a high index of suspicion for infection, and conduct early, thorough diagnostic work-up coupled with prompt institution of antimicrobial therapy. Detailed individualized infection risk assessments are central to guiding therapeutic care pathways and optimizing clinical outcomes.

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