Published in final edited form as:

Emerg Med Clin North Am. 2018 November ; 36(4): 811–822. doi:10.1016/j.emc.2018.06.010.

Approach to Transplant Infectious Diseases in the Emergency Department

Diana Zhong, MD and

Department of Medicine, University of Washington, Seattle, WA

Stephen Y. Liang, MD, MPHS

Divisions of Emergency Medicine and Infectious Diseases, Washington University School of Medicine, St. Louis, MO

Summary

The emergency department (ED) is an increasingly important site of care for patients who have undergone solid organ transplantation (SOT) or hematopoietic cell transplantation (HCT). SOT and HCT patients can be challenging and daunting to care for due to their medical complexity and increased risk for severe and life-threatening infections. It is paramount for emergency physicians to recognize infections early on, obtain appropriate diagnostic testing, initiate empiric antimicrobial therapy, and consider specialty consultation and inpatient admission when caring for these patients. This review provides emergency physicians with an approach to the assessment of a transplant patient's underlying risk for infection, formulation of a broad differential diagnosis, and initial management of transplant infectious disease emergencies in the ED.

Keywords

Solid organ transplantation; Hematopoietic cell transplantation; Infectious diseases; Emergency Department

Introduction

Modern advances in solid organ and hematopoietic cell transplantation, including breakthroughs in surgical technique and immunosuppression, have significantly improved survival and long-term clinical outcomes. As the multidisciplinary field of transplantation

Stephen Y. Liang, MD, MPHS (corresponding author), 4523 Clayton Avenue, Campus Box 8051, St. Louis, MO 63110, USA, syliang@wustl.edu.

Author Contact Information: Diana Zhong, MD, 1959 NE Pacific Street, Box 356429, Seattle, WA 98195, USA, zhongd@uw.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure Statement

D.Z. reports no conflicts of interest and no financial disclosures in this work. S.Y.L. reports no conflicts of interest in this work. S.Y.L. is the recipient of a KM1 Comparative Effectiveness Research Career Development Award (KM1CA156708-01) and received support through the Clinical and Translational Science Award (CTSA) program (UL1RR024992) of the National Center for Advancing Translational Sciences as well as the Barnes-Jewish Patient Safety & Quality Career Development Program, which is funded by the Foundation for Barnes-Jewish Hospital.

medicine continues to evolve and innovate, those who have undergone a transplant will continue to be some of the most medically complex and severely immunocompromised patients an emergency physician will care for in the emergency department (ED).

Solid organ transplantation (SOT) is the surgical placement or replacement of a donated organ to address end-stage organ failure. In 2017, 34,770 SOTs were performed in the U.S. alone, a number that has continued to rise annually. [1, 2] While kidneys remain the most frequently transplanted organ to date, heart, liver, pancreas, lung, and intestinal transplantation have also become increasingly common over the past decade. [2, 3]

Hematopoietic cell transplantation (HCT) encompasses the introduction of hematopoietic progenitor cells to restore function to failing bone marrow or immune systems. It is performed for a wide range of indications including leukemia, lymphoma, multiple myeloma, and certain non-malignant diseases (*e.g.*, sickle cell disease, immunodeficiency diseases). In 2016, the most common indications for HCT in U.S. were multiple myeloma and lymphoma, comprising 63% of all HCTs. [4] HCT is categorized by donor type (allogeneic *vs.* autologous) and source of progenitor cells (bone marrow, peripheral blood, or umbilical cord blood). In allogeneic transplantation, hematopoietic cells are derived from a relative or unrelated donor. In autologous transplants, cells are harvested from a patient's own body. In 2015, 12,570 autologous HCTs, 3,804 related donor allogeneic HCTs, and 4,918 unrelated donor allogeneic HCTs were performed in the U.S. [5]

Emergency departments play a critical role in post-transplantation care. [6] At one high-volume transplant center, nearly 40% of abdominal organ transplant recipients sought ED care within one year after transplantation, with three-quarters of visits resulting in hospital admission. [7] In California, Florida, and New York, 57% of patients who underwent kidney transplantation visited an ED within the first two years after implant and almost half of these ED visits resulted in hospitalization. [8] While ED utilization by HCT patients has not been well-quantified, it is likely to be significant. Many similarities exist between SOT and HCT patients when it comes to the need for long-term immunosuppression, rendering both populations distinctly vulnerable to infectious diseases. Conversely, certain aspects also set these two populations apart. In this review, we will provide emergency physicians with an approach to assessing a transplant patient's underlying risk for infection, creating a broad differential of infectious diseases suited to that risk, and managing their initial infectious disease care in the ED.

General principles

Infections are common in patients who have undergone SOT and HCT. Infections after SOT are often from surgical complications, and later from chronic immunosuppression to prevent graft rejection. Infections after HCT relate to chemotherapy and sometimes radiation used to eliminate the underlying malignancy and ensuing immunosuppression to prevent donor graft rejection. Depending on the depth of immunosuppression required, both SOT and HCT patients may be vulnerable to opportunistic pathogens, including viruses and fungi. Should SOT patients experience graft rejection or HCT patients develop graft-versus-host disease (GVHD), additional immunosuppression may be necessary, further increasing their susceptibility to infection. In GVHD, T-cells present in the donor graft are activated,

recognize the recipient (host) as foreign, and mount an immune reaction against host tissues (e.g., skin, liver, gastrointestinal tract). Significant healthcare exposure at the time of and after transplantation also increases the risk of infection due to nosocomial pathogens.

Generally speaking, the risk of infection after SOT or HCT is greatest immediately after the procedure. Incidence of infection ranges anywhere from 25% to 80% during the critical first year following SOT. [9] Infection accounts for 20% of all deaths occurring within the first 100 days after HCT among those who have undergone HLA-matched sibling or unrelated donor allogeneic transplantation. [4] In a study that followed HCT patients for 30 months post procedure, 93% experienced infections, with more than half involving the bloodstream. [10] Infections after SOT or HCT can be severe and even life-threatening. The incidence of sepsis is 20% to 60% among SOT recipients, with in-hospital mortality ranging from 5% to 40%. [11] Infections significantly influence long-term transplant outcomes, endangering graft survival and contributing to chronic rejection. [12] A significant proportion of post-transplantation ED visits are due to infectious complications; almost half result in hospital admission. [6–8, 13–15]

Four basic principles can help guide the emergency physician's approach to infectious disease emergencies in the post-transplantation patient:

- 1) Beware of atypical clinical presentations and findings of infection.
- 2) Establish the timeline since transplantation and use this as a guide for building a differential of potential infectious diseases along the continuum of immunosuppression.
- 3) While infections are common and wide-ranging after transplantation, maintain a broad differential that includes non-infectious causes of fever in this population.
- 4) Recognize critical infection, initiate timely antimicrobial therapy and resuscitation when indicated, and understand that a full infectious disease evaluation often requires inpatient admission.

Atypical clinical presentations of infection after transplantation

Recognizing the signs and symptoms of infection in SOT and HCT patients can be challenging. Immunosuppressive therapy can impair the inflammatory response, and thus a transplant patient may not exhibit a classic physiologic response to infection. Up to 40% of infections in this population will present without a fever. [9 16] Subtle symptoms such as a mild cough or scant diarrhea can mask a serious underlying infection. In SOT patients, altered anatomy after surgery further mutes the usual physical manifestations of infection. In lung transplant recipients, airway defense mechanisms are compromised by surgical denervation, decreased mucociliary clearance, and blunted cough reflex. As a result, patients with pneumonia of their transplanted lungs may not develop a significant cough. [17] Renal transplants are often heterotopic, meaning the graft is implanted in a different location, usually the iliac fossa. Pyelonephritis involving the transplanted kidney will therefore present with pain localized to that site rather than costovertebral angle tenderness associated with infection of a native kidney. Laboratory and other diagnostic testing in SOT and HCT patients with infection may also be less revealing than that of immunocompetent patients

due to impaired inflammatory responses. [18 19] Leukocytosis is often absent. On chest radiography, infiltrates may be absent or minimal in the setting of pneumonia. [20] Pyuria can be absent despite a urinary tract infection. A paucity of classic findings indicating infection should not dissuade an emergency physician from further clinical investigation if the index of suspicion for infection is high based on a patient's level of immunosuppression.

Transplantation timelines and creating the infectious disease differential

Unique temporal frameworks help characterize the phases of immunosuppression following SOT and HCT. Each phase carries its own inherent risk for certain infections, although exceptions frequently exist to the rule. Both timelines start with the initial transplant and proceed along a continuum of immunosuppression to prevent graft rejection, tailored to each patient's unique clinical situation.

A patient's "net state of immunosuppression" is determined by their immunosuppressive regimen, underlying disease process, medical comorbidities, use of antimicrobial prophylaxis, and other risk factors (*e.g.*, chronic urinary catheter, vascular access device). [9 21] Most patients receive antimicrobial prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) (*e.g.*, trimethoprim/sulfamethoxazole, dapsone, or inhaled pentamidine) and cytomegalovirus (CMV) (*e.g.*, valganciclovir). [22] Antifungal prophylaxis can vary. Fluconazole is used primarily for *Candida* prophylaxis; voriconazole and itraconazole for broader coverage against *Candida*, *Aspergillus*, and most molds; posaconazole has the widest spectrum of coverage, including *Candida*, *Aspergillus*, and mucormycosis. [23] The risk of an opportunistic infection (OI) increases as immunosuppression increases, usually within a month after transplantation.

Most transplant patients with an uncomplicated clinical course will see their immunosuppression decreased over time. As a result, their risk for infection will return closer to "normal" as they transition to maintenance immunosuppression. [21] However, those with complications including graft rejection or GVHD often require continuation or intensification of their immunosuppression, prolonging their vulnerability to infection.

Infections after Solid Organ Transplantation

The timeline for infection after SOT can be broken down into three phases: early (<1 month post-transplantation), intermediate (1–6 months post-transplantation), and late (>6 months post-transplantation).

Early (<1 month post-transplantation): Many infections occurring immediately after SOT are related to surgery and hospitalization. During the post-operative period, it is important to consider surgical site infections and anastomotic stenosis or leaks. In one study, 15% of renal transplant patients developed a surgical site infection. [24] Bile leaks occur in up to 20% of liver transplant patients, often at the anastomotic site, and typically present early on, while other surgical complications (*e.g.*, biliary strictures) arise later. [25] In kidney transplantation patients, urinary tract infections (UTI) are the most common bacterial infection requiring hospitalization. Patients may be further predisposed to UTIs if they have complications such as ureteral stricture or obstruction. [12, 26] Healthcare-associated

infections due to medical devices, including central line-associated bloodstream infection (CLABSI) and catheter-associated urinary tract infection (CAUTI), are also possible. Infections due to antibiotic-resistant organisms are common, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), as well as healthcare-associated organisms such as *Clostridium difficile*, and resistant *Candida* species, particularly in the setting of prolonged hospitalization and antibiotic exposure. *C. difficile* infection affects up to 30% of SOT patients, often with severe disease. Depending on the season, respiratory viruses including RSV and influenza can be nosocomially acquired. [22, 27]

Donor-derived infections are another important consideration during the early post transplantation period. The serologic status of the donor and recipient to various organisms [e.g., CMV, Epstein-Barr virus (EBV), *Toxoplasma gondii*] can aid the assessment of infection risk, although this information may not be readily available in the ED. Donor allografts can become contaminated or colonized with fungi (e.g., *Aspergillus*) or bacteria (e.g., MRSA). Less commonly, grafts may harbor viruses [e.g., West Nile virus, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)], *Mycobacterium tuberculosis*, or endemic fungi such as *Histoplasma*. [22, 27] Toxoplasmosis is the most common protozoal infection in SOT patients. [28] Patients with toxoplasmosis may be asymptomatic or present with nonspecific symptoms such as fever and lymphadenopathy. Central nervous system toxoplasmosis usually presents as encephalitis. Toxoplasmosis can also manifest as myocarditis, interstitial pneumonitis, or chorioretinitis. Transmission of *Toxoplasma* infection from a seropositive donor to a seronegative recipient is greatest in heart transplant patients, with up to 75% developing toxoplasmosis in the absence of prophylaxis. [29] *Strongyloides* infection can often be innocuous initially, but carries a mortality rate of 50% to 80% in the setting of hyperinfection syndrome or rapid acceleration of infection due to immunosuppression. Hyperinfection syndrome presents as rash, abdominal pain, and pneumonitis, but may also masquerade with a bacterial superinfection in the form of Gram-negative meningitis and bacteremia. [28 30] Chagas disease, an infection due to *Trypanosoma cruzi*, can present with myocarditis, encephalitis, or cutaneous manifestations (e.g., panniculitis). [28]

Intermediate (1–6 months post-transplantation): Opportunistic infections abound during the intermediate phase due to prolonged immunosuppression. SOT patients are at increased risk for viral infections, including primary infection and reactivation of latent infections. CMV syndrome can present with fever, weakness, myalgia, arthralgia, and myelosuppression with viremia. Tissue-invasive CMV disease can affect any organ, most commonly causing pneumonitis, as well as enteritis, hepatitis, meningoencephalitis, and retinitis. Disseminated CMV infection can be fatal. Finally, CMV infection can lead to early or late rejection of renal transplants, cardiac vasculopathy in heart transplants, and bronchiolitis obliterans in lung transplants. [22 27]

EBV is another important viral infection, and may present initially with fever, malaise, fatigue, weight loss, and lymphadenopathy. EBV infection can be complicated by post transplant lymphoproliferative disorder (PTLD), a disease with varied presentations ranging from benign polyclonal B-cell proliferation to malignant B-cell lymphoma. Suspect PTLD

in patients who present with constitutional symptoms and extra-nodal masses. The risk of PTLT is greatest in EBV-negative recipients who develop a primary infection. [31]

Other viral infections can include herpes simplex virus (HSV), HBV, HCV, human T-lymphotropic virus (HTLV), and polyomaviruses. BK virus is a notable polyomavirus in renal transplant patients that can cause nephropathy or hemorrhagic cystitis. Patients with polyomavirus-associated nephropathy will typically present with renal dysfunction, sometimes with ureteral obstruction from stenosis or stricture. [26] JC virus, another polyomavirus, is the etiologic agent for progressive multifocal leukoencephalopathy (PML), a severe demyelinating disease of the central nervous system. Symptoms of PML can include visual disturbances, hemiparesis, and behavioral changes. [22 27 32]

Opportunistic fungal infections during the intermediate period include *Pneumocystis jirovecii* pneumonia (PJP), *Nocardia*, *Cryptococcus*, *Aspergillus*, mucormycosis, *Candida*, and endemic fungi. *Aspergillus* is the most common cause of respiratory fungal infection, but may present as disseminated disease. [33] Mucormycosis, due to *Rhizopus*, *Mucor*, or *Rhizomucor* spp., classically manifests as rhinoorbital-cerebral disease with symptoms of acute sinusitis, fever, nasal ulceration and necrosis, periorbital or facial swelling, decreased vision, ophthalmoplegia, and headache, with the potential for cerebral extension. Isolated pulmonary mucormycosis presents as fever and hemoptysis. Candidemia can be associated with septic shock, which carries a high mortality. *Candida* can also cause intra-abdominal infections, including peritonitis and abdominal abscesses. [34] Endemic fungi, including *Histoplasma*, *Blastomyces*, and *Coccidioides*, should be considered depending on donor and recipient geographic risk factors and exposure history.

Bacterial and mycobacterial infections, including those due to *Listeria monocytogenes* and *Mycobacterium tuberculosis*, are also possible during the intermediate phase. [11, 12] SOT patients have an increased risk of bacterial meningitis, most commonly caused by *Streptococcus pneumoniae* and *L. monocytogenes*. [35] In one study, SOT patients had a 110-fold increased risk of *Listeria* infection compared to the general population. [36] The frequency of tuberculosis in SOT patients is 20 to 70 times greater than that of the general population. Most cases of tuberculosis in SOT patients result from reactivation of latent infection after initiation of immunosuppression. [37]

Late post-transplantation (6 months after transplantation): As immunosuppression is tapered to maintenance doses, the types of infection encountered in SOT patients begin to resemble those encountered in community-dwellers. Nevertheless, SOT patients still bear a comparatively higher risk of infection due to community acquired and opportunistic pathogens. Community-acquired pathogens include common respiratory viruses such as influenza and RSV [38], as well as bacteria including *S. pneumoniae*, *Mycoplasma*, *Legionella*, and *Listeria*. [22] Urinary tract infections are also common, particularly among renal transplant patients. [39, 40]

Cryptococcal infections frequently present after the first year, manifesting as central nervous system infection, pulmonary infection, or disseminated infection. CNS cryptococcal infections vary in presentation in HIV-negative patients, ranging from months of subacute

symptoms to acute illness within days. Most commonly, patients will present with a subacute meningoencephalitis with fever, headache, lethargy, personality changes, and memory loss. Pulmonary infection can present as pneumonia or with severe illness including acute respiratory distress syndrome (ARDS). [33]

Infections after Hematopoietic Cell Transplantation

In many ways, the timeline of infection after HCT mirrors that of SOT patients. After transplantation, immune constitution typically occurs several months after autologous HCT but often a year or longer following allogeneic HCT. In patients who develop chronic GVHD, immune reconstitution may be dramatically delayed or never occur. [41] Donor source and degree of donor-recipient HLA compatibility also impede immune reconstitution. [42] As with SOT patients, the timeline after HCT can be divided into three phases: pre-engraftment (transplant to neutrophil recovery, or about <15–45 days after HCT), early post-engraftment (day 30 to day 100), and late post-engraftment (after day 100). [43]

Pre-engraftment (transplant to neutrophil recovery, <15–45 days after HCT): This period is marked by significant neutropenia as well as mucocutaneous damage (e.g., mucositis). Patients are at increased risk for bacteremia, particularly due to Gram-negative organisms, as a consequence of mucosal translocation. [43] Neutropenic fever in a HCT patient can be an indication of a life-threatening infection and is considered a medical emergency. [44] HCT patients are also at increased risk for reactivation of HSV as well as fungal infections including *Candida* and *Aspergillus*. [41] Diarrhea should raise a concern for *C. difficile* infection, which frequently occurs before engraftment in the setting of neutropenia and antimicrobial use. [10] Oftentimes, patients may still have indwelling central venous catheters during this period, predisposing them to bloodstream infection. [41] In one study of HCT patients diagnosed with bacteremia, 56% were due to Gram-positive and 21% were due to Gram-negative bacteria, with *Pseudomonas aeruginosa* being the predominant organism in the latter group. Mortality is significantly higher in HCT patients who develop Gram-negative bacteremia. [10]

Early post-engraftment (day ~30 to day 100 after HCT): Impaired cell-mediated immunity dominates during this phase as immunosuppression sets in. A diagnosis of acute GVHD may require escalation of immunosuppressive therapy, further increasing the depth of immunosuppression. Viral infections are common, including herpesviruses such as CMV and EBV, as well as BK virus. In one study, CMV was the most common viral infection diagnosed in HCT patients. [10] Fungal infections such as PJP and *Aspergillus* are likewise frequent. [41–43] Some HCT patients may have residual mucocutaneous damage with persistent neutropenia, rendering them prone to the types of infections encountered during the pre-engraftment period.

Late post-engraftment (day ~30 to day 100 after HCT): Patients with chronic GVHD requiring prolonged and increased immunosuppression remain at highest risk for infection, particularly involving CMV and EBV, similar to the early postengraftment phase, as well as VZV. They are also vulnerable to infection with encapsulated bacteria (e.g., *S. pneumoniae*) [43], PJP, and *Aspergillus*. [41]

The frequency of tuberculosis in HCT patients is 10 to 40 times higher than that of the general population. Risk factors include allogeneic transplantation from an unrelated donor, chronic GVHD (and resultant immunosuppressive treatment with corticosteroids), unrelated or mismatched allograft, and use of certain conditioning regimens; the type and severity of the patient's underlying primary hematological disorder also influences their risk for tuberculosis. [37]

Non-infectious causes of fever in the transplant patient

Although infectious diseases are a common cause of fever in SOT and HCT patients, it is important to maintain a broad differential diagnosis that also encompasses non-infectious etiologies. Graft rejection, thrombosis, adverse medication effects, and malignancy are all potential causes of fever in this high-risk patient population. [45] In HCT, symptoms such as diarrhea or rash may represent GVHD rather than infection; however, infection must be ruled out first as a cause of these symptoms. [42]

Initial Management in the Emergency Department

Initial ED evaluation and management of infectious disease in the SOT or HCT patient should focus on three priorities: recognizing the severity of the infection, identifying its source, and initiating appropriate antimicrobial therapy and resuscitation in a timely manner.

Sepsis and neutropenic fever are imminently life-threatening infectious disease emergencies in the post-transplantation patient. Both are time-sensitive diagnoses that require expedited collection of microbiologic cultures and early administration of empiric antibiotics. To this effect, initial ED assessment of the SOT or HCT patient must focus on recognizing these two conditions quickly. Clinical criteria for sepsis and septic shock in SOT and HCT patients are no different than that of the general population codified in current international guidelines. [46 47] Tools such as the quick Sequential Organ Failure Assessment (qSOFA) may assist in identifying critically-ill patients but remain under active investigation in settings outside of the intensive care unit, and have not been widely studied in SOT or HCT populations. [48, 49] Neutropenic fever is defined by an absolute neutrophil count (ANC) of <500 cells/mm³ or $<1,000$ cells/mm³ with an anticipated decline to <500 cells/mm³ over the next 48 hours in the presence of a single oral temperature measurement of $\geq 38.3^{\circ}\text{C}$ (101°F) or a temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F) sustained over a 1-hour period. [44] Some patients may have "functional neutropenia," a condition in which malignancy or medical therapy cause qualitative neutrophil defects that increase a patient's risk of infection despite a "normal" neutrophil count.

ED evaluation of the SOT or HCT patient should begin with a complete blood cell (CBC) count with differential, comprehensive chemistry panel, urinalysis, and chest radiograph at a minimum. If sepsis or a bloodstream infection is suspected, at least two sets of blood cultures should be obtained from different sites immediately and prior to the administration of antibiotics, whenever possible. [47] If the patient has a central venous catheter, blood cultures should be drawn from each catheter lumen and from a peripheral site. [50] Fungal blood cultures should be considered in patients that are neutropenic or otherwise at high risk for developing an invasive fungal infection. [44]

A thorough physical examination is necessary to identify and investigate potential sources of infection. Microbiologic cultures should be obtained from appropriate sites (*e.g.*, sputum, urine, wound/abscess) in the presence of localizing signs and symptoms of infection. In patients with concern for respiratory infection, respiratory virus testing (including influenza and RSV) should be performed. Based on patient presentation, risk factors, and laboratory assay availability, urinary antigen testing for *S. pneumoniae*, *Legionella*, and *Histoplasma* can aid diagnosis. In patients presenting with diarrhea and a recent history of antibiotic exposure, stool testing for *C. difficile* infection should be pursued. Serum biomarkers for *Aspergillus* and other fungal infections, including galactomannan antigen or beta-D-glucan, disease-specific serologies, and specialized polymerase chain reaction (PCR) assays can help expand the ED workup but are best ordered in consultation with an infectious disease specialist. [18]

Computed tomography (CT) of the brain and lumbar puncture should be considered in SOT and HCT patients with suspected CNS infection. Magnetic resonance imaging (MRI) is appropriate when looking for signs of opportunistic CNS infections, including PML. In patients with pulmonary complaints and increased risk for invasive pulmonary aspergillosis or other OIs, emergency physicians should have a low threshold for obtaining a CT of the chest. [33] In neutropenic patients with fever, abdominal pain, and diarrhea, a CT of the abdomen and pelvis should be performed to evaluate for neutropenic enterocolitis, also known as typhilitis. [51–52] Neutropenic enterocolitis is life-threatening infection of the cecum, ileum, and sometimes the ascending and transverse colon.

Empiric antimicrobial therapy in the ED for sepsis, neutropenic fever, and other serious undifferentiated infection should broadly cover Gram-positive and Gram-negative bacteria using an anti-pseudomonal agent (*e.g.*, cefepime, meropenem, or piperacillin-tazobactam). If there is a concern for infection due to methicillin-resistant *Staphylococcus aureus* (*e.g.*, central line associated bloodstream infection, skin and soft tissue infection, pneumonia, critical illness, hemodynamic instability), additional Gram-positive coverage should be added (*e.g.*, vancomycin). If a patient has risk factors for infection or has had a history of colonization or infection due to antibiotic-resistant bacteria (*e.g.*, MRSA, VRE, resistant Gram-negative bacteria), empiric coverage directed against these organisms may be considered. [44] When available, hospital antibiograms can provide invaluable guidance in selecting empiric antibiotics with low observed resistance rates for specific organisms (*e.g.*, *P. aeruginosa*). Likewise, review of a patient's medical record and prior microbiologic data can also help direct empiric therapy.

Antifungal therapy with empiric liposomal amphotericin B should be initiated if a rapidly progressive acute pulmonary process or disseminated fungal infection is suspected. [33] For less critically-ill patients with suspicion for fungal infections, other less toxic antifungal agents can be considered. First-line therapy for invasive aspergillosis is voriconazole, although isavuconazole and posaconazole are options as well. Echinocandins are sometimes added for synergistic effect. [17–33] If *Candida* infection is suspected, the empiric therapy of choice is an echinocandin, such as micafungin or caspofungin. Azoles (*e.g.*, fluconazole) should be avoided as first-line empiric therapy due to increasing resistance. [47–53] In

patients with concern for mucormycosis, empiric therapy with liposomal amphotericin B is appropriate.

In patients with sepsis and those with neutropenic fever, broad-spectrum antimicrobial therapy should be administered as soon as possible, preferably within one hour of recognition. [46] Source control (*e.g.*, abscess drainage, removal of an infected central venous catheter or urinary catheter, surgical debridement for rhino-orbital-cerebral mucormycosis) should likewise ensue quickly. Volume resuscitation (30 mL/kg IV of crystalloid solution within the first 3 hours) and vasopressor therapy should be initiated in the face of sepsis and septic shock adhering to current guidelines and best practices. [46 47]

Critically-ill SOT and HCT patients should be admitted to the hospital for further resuscitation, antibiotic therapy, and diagnostic evaluation. The decision to admit a clinically stable patient can be more nuanced, and patient dispositions are best made in consultation with specialists in infectious diseases, transplantation medicine, and/or hematology/oncology as appropriate. Scoring systems for certain infectious diseases can help inform admission decisions. For example, in the case of pneumonia, CURB-65 [Confusion, Uremia (blood urea nitrogen >7 mmol/L or 19mg/dL), Respiratory rate (≥ 30 breaths/minute), Blood pressure (systolic <90 mmHg or diastolic ≥ 60 mmHg), age ≥ 65 years] and Pneumonia Severity Index (PSI) can be used to identify high-risk patients requiring hospitalization. However, it is important to understand that neither scoring system takes into account immunosuppression or transplantation as a risk factor for severe disease. Consequently, emergency physicians must rely upon clinical judgment and a global risk assessment to safely and appropriately manage these complex patients. [18] Serious infections in SOT and HCT patients can present with subtle symptoms that have the potential to progress rapidly. Therefore, emergency physicians should have a lower threshold to admit these patients for more specialized inpatient evaluation (*e.g.*, bronchoscopy, fluid aspiration, tissue biopsy) and management, including adjustment of immunosuppression.

Conclusion

The approach to transplant-related infectious diseases can be daunting and challenging, given the broad range of infections possible along a complex spectrum of immunosuppression. This is compounded by the fact that infections in SOT and HCT patients often present differently than in the immunocompetent host. Opportunistic infections are common. A temporal framework of transplantation and ensuing immunosuppression helps emergency physicians assess a post-transplantation patient's overall risk for different types of infection over time. Timely evaluation, management, and disposition from the ED should hinge on a thorough history and physical examination, laboratory testing, imaging, and specialty consultation, along with empiric antimicrobial therapy and resuscitation when clinically appropriate.

References

1. National Data. Secondary National Data March 29, 2018. 2018 Available at:<https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>. Accessed March 29, 2018.

2. National Data: Transplants By Organ Type January 1, 1988-February 28, 2018 Available at: <https://unos.org/data/>. Accessed March 29, 2018.
3. OPTN/SRTR 2016 annual data report: introduction. *Am J Transplant* 2018;18(Suppl 1):10–17. [PubMed: 29292601]
4. D'Souza AFC. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides. Secondary Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides 2017 Available at: <http://www.cibmtr.org/>. Accessed March 29, 2018.
5. Transplant Activity Report. Secondary Transplant Activity Report April 15, 2017. 2017 Available at: https://bloodcell.transplant.hrsa.gov/research/transplant_data/transplant_activity_report/index.html. Accessed March 29, 2018.
6. Li AH, Lam NN, Naylor KL, et al. Early hospital readmissions after transplantation: burden, causes, and consequences. *Transplantation* 2016;100(4):713–8. [PubMed: 26469984]
7. McElroy LM, Schmidt KA, Richards CT, et al. Early postoperative emergency department care of abdominal transplant recipients. *Transplantation* 2015;99(8):1652–7. [PubMed: 26050012]
8. Schold JD, Elfadawy N, Buccini LD, et al. Emergency department visits after kidney transplantation. *Clin J Am Soc Nephrol* 2016;11(4):674–83. [PubMed: 27012951]
9. Long B, Koyfman A. The emergency medicine approach to transplant complications. *Am J Emerg Med* 2016;34(11):2200–8. [PubMed: 27645810]
10. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in hematopoietic cell transplant recipients: results from the organ transplant infection project, a multicenter, prospective, cohort study. *Open Forum Infect Dis* 2017;4(2):ofx050.
11. Florescu DF, Sandkovsky U, Kalil AC. Sepsis and challenging infections in the immunosuppressed patient in the intensive care unit. *Infect Dis Clin North Am* 2017;31(3):415–34. [PubMed: 28687212]
12. Arpali E, Al-Qaoud T, Martinez E, et al. Impact of ureteral stricture and treatment choice on long-term graft survival in kidney transplantation. *Am J Transplant* 2018 <https://doi.org/10.1111/ajt.14696>.
13. Savitsky EA, Votey SR, Mebust DP, et al. A descriptive analysis of 290 liver transplant patient visits to an emergency department. *Acad Emerg Med* 2000;7(8):898–905. [PubMed: 10958130]
14. Unterman S, Zimmerman M, Tyo C, et al. A descriptive analysis of 1251 solid organ transplant visits to the emergency department. *West J Emerg Med* 2009;10(1):48–54. [PubMed: 19561769]
15. Dalrymple LS, Romano PS. Emergency department visits after kidney transplantation. *Clin J Am Soc Nephrol* 2016;11(4):555–7. [PubMed: 27012952]
16. Sawyer RG, Crabtree TD, Gleason TG, et al. Impact of solid organ transplantation and immunosuppression on fever, leukocytosis, and physiologic response during bacterial and fungal infections. *Clin Transplant* 1999;13(3):260–5. [PubMed: 10383107]
17. Adegunsoye A, Strek ME, Garrity E, et al. Comprehensive care of the lung transplant patient. *Chest* 2017;152(1):150–64. [PubMed: 27729262]
18. Pagalilauan GL, Limaye AP. Infections in transplant patients. *Med Clin North Am* 2013;97(4):581–600. [PubMed: 23809715]
19. Pelletier SJ, Crabtree TD, Gleason TG, et al. Characteristics of infectious complications associated with mortality after solid organ transplantation. *Clin Transplant* 2000;14(4 Pt 2):401–8.
20. Wilmes D, Coche E, Rodriguez-Villalobos H, et al. Bacterial pneumonia in kidney transplant recipients. *Respir Med* 2018;137:89–94. [PubMed: 29605219]
21. Fishman JA. Infections in immunocompromised hosts and organ transplant recipients: essentials. *Liver Transpl* 2011;17(Suppl 3):S34–7.
22. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357(25):2601–14. [PubMed: 18094380]
23. Patel TS, Eschenauer GA, Stuckey LJ, et al. Antifungal prophylaxis in lung transplant recipients. *Transplantation* 2016;100(9):1815–26. [PubMed: 26950711]
24. Harris AD, Fleming B, Bromberg JS, et al. Surgical site infection after renal transplantation. *Infect Control Hosp Epidemiol* 2015;36(4):417–23. [PubMed: 25782896]

25. Senter-Zapata M, Khan AS, Subramanian T, et al. Patient and graft survival: biliary complications after liver transplantation. *J Am Coll Surg* 2018;226(4):484–94. [PubMed: 29360615]
26. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012;7(12):2058–70. [PubMed: 22977217]
27. Green M Introduction: infections in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):3–8.
28. Franco-Paredes C, Jacob JT, Hidron A, et al. Transplantation and tropical infectious diseases. *Int J Infect Dis* 2010;14(3):e189–96. [PubMed: 19647464]
29. Khurana S, Batra N. Toxoplasmosis in organ transplant recipients: evaluation, implication, and prevention. *Trop Parasitol* 2016;6(2):123–8. [PubMed: 27722100]
30. Coster LO. Parasitic infections in solid organ transplant recipients. *Infect Dis Clin North Am* 2013;27(2):395–427. [PubMed: 23714347]
31. Allen UD, Preiksaitis JK, AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):107–20. [PubMed: 23465004]
32. Polyomaviruses Cook L. *Microbiol Spectr* 2016;4(4). <https://doi.org/10.1128/microbiolspec.DMIH2-0010-2015>.
33. De La Cruz O, Silveira FP. Respiratory fungal infections in solid organ and hematopoietic stem cell transplantation. *Clin Chest Med* 2017;38(4):727–39. [PubMed: 29128021]
34. Saxena S, Gee J, Klieger S, et al. Invasive fungal disease in pediatric solid organ transplant recipients. *J Pediatric Infect Dis Soc* 2017 <https://doi.org/10.1093/jpids/pix041>.
35. van Veen KE, Brouwer MC, van der Ende A, et al. Bacterial meningitis in solid organ transplant recipients: a population-based prospective study. *Transpl Infect Dis* 2016;18(5):674–80. [PubMed: 27385317]
36. Qayyum QJ, Scerpella EG, Moreno JN, et al. Report of 24 cases of *Listeria monocytogenes* infection at the University of Miami Medical Center. *Rev Invest Clin* 1997;49(4):265–70. [PubMed: 9707990]
37. Aguado JM, Silva JT, Samanta P, et al. Tuberculosis and transplantation. *Microbiol Spectr* 2016;4(6). <https://doi.org/10.1128/microbiolspec.TNMI7-0005-2016>.
38. Paulsen GC, Danziger-Isakov L. Respiratory viral infections in solid organ and hematopoietic stem cell transplantation. *Clin Chest Med* 2017;38(4):707–26. [PubMed: 29128020]
39. Uysal E, Dokur M, Bakir H, et al. The reasons of renal transplant recipients' admission to the emergency department; a case series study. *Emerg (Tehran)* 2016;4(4):207–10. [PubMed: 27800542]
40. Trzeciak S, Sharer R, Piper D, et al. Infections and severe sepsis in solid-organ transplant patients admitted from a university-based ED. *Am J Emerg Med* 2004;22(7):530–3. [PubMed: 15666255]
41. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. *Infect Dis Clin North Am* 2010;24(2):257–72. [PubMed: 20466269]
42. Socie G, Ritz J. Current issues in chronic graft-versus-host disease. *Blood* 2014;124(3):374–84. [PubMed: 24914139]
43. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* 2009;15(10):1143–238. [PubMed: 19747629]
44. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011;52(4):e56–93. [PubMed: 21258094]
45. Venkat KK, Venkat A. Care of the renal transplant recipient in the emergency department. *Ann Emerg Med* 2004;44(4):330–41. [PubMed: 15459617]
46. Howell MD, Davis AM. Management of sepsis and septic shock. *JAMA* 2017;317(8):847–8. [PubMed: 28114603]
47. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45(3):486–552. [PubMed: 28098591]

48. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic accuracy of sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. *JAMA* 2017;317(3):301–8. [PubMed: 28114554]
49. Haydar S, Spanier M, Weems P, et al. Comparison of QSOFA score and SIRS criteria as screening mechanisms for emergency department sepsis. *Am J Emerg Med* 2017;35(11):1730–3. [PubMed: 28712645]
50. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;49(1):1–45. [PubMed: 19489710]
51. Lebon D, Biard L, Buyse S, et al. Gastrointestinal emergencies in critically ill cancer patients. *J Crit Care* 2017;40:69–75. [PubMed: 28363097]
52. Rodrigues FG, Dasilva G, Wexner SD. Neutropenic enterocolitis. *World J Gastroenterol* 2017;23(1):42–7. [PubMed: 28104979]
53. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;62(4):e1–50. [PubMed: 26679628]

Key Points

- Patients who have undergone solid organ transplantation (SOT) or hematopoietic cell transplantation (HCT) are medically complex and at high risk of infection.
- Transplant patients can present with subtle or atypical presentations of infection, therefore emergency physicians must maintain a high index of suspicion for infection.
- The infectious differential for post-transplant patients is broad, but can be guided by a timeline of immunosuppression.
- Patients who are critically ill or have potentially life-threatening infections should be managed and resuscitated appropriately and in a timely manner, through targeted laboratory testing and imaging, broad-spectrum antimicrobials, resuscitation, specialty consultation, and hospital admission.