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TRANSPLANT AND ONCOLOGY (M ISON AND N THEODOROPOULOS, SECTION EDITORS)

Sepsis in the Severely Immunocompromised Patient

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Abstract The prevention and treatment of sepsis in the immunocompromised host present a challenging array of diagnostic and management issues. The neutropenic patient has a primary defect in innate immune responses and is susceptible to conventional and opportunistic pathogens. The solid organ transplant patient has a primary defect in adaptive immunity and is susceptible to a myriad of pathogens that require an effective cellular immune response. Risk for infections in organ transplant recipients is further complicated by mechanical, vascular, and rejection of the transplanted organ itself. The immune suppressed state can modify the cardinal signs of inflammation, making accurate and rapid diagnosis of infection and sepsis difficult. Empiric antimicrobial agents can be lifesaving in these patients, but managing therapy in an era of progressive antibiotic resistance has become a real issue. This review discusses the challenges faced when treating severe infections in these high-risk patients.

Keywords Sepsis · Septic shock · Neutropenia · Neutropenic fever · Immunocompromised host · Solid organ transplant infections

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Introduction

The severely immunocompromised patient is at increased risk of infection by common pathogens, as well as opportunistic infections by less virulent microorganisms of little concern to immunocompetent hosts. This omnipresent risk of infection predisposes to increased risk of developing systemic compromise, including sepsis and septic shock [1, 2]. Sepsis in the adult patient with underlying acquired, immune suppression will be the focus of this review. The most common cause of severe, prolonged, immune compromise is cytoablative chemotherapy as a treatment for some forms of neoplastic disease (e.g., induction chemotherapy for acute leukemia and lymphoreticular malignancies), delayed bone marrow recovery following allogenic hematopoietic stem cell transplantation (HSCT), and solid organ transplantation. Less intensive chemotherapeutic regimens with low incidence of neutropenia and short duration of bone marrow depression, such as those regimens used for many solid organ malignancies pose little risk of systemic infection or sepsis. These patients are often managed as outpatients and have an excellent short-term prognosis [3, 4]. Paradoxically, despite the excess incidence of infections in the severely immunocompromised patients, the prognosis for those patients who do develop sepsis appears to be no worse or perhaps even better than their non-immunocompromised counterparts [2–5, 6•]. The reason(s) for these unexpected findings will be discussed along with some proposed new strategies that might further reduce mortality from sepsis in patients with immunosuppression.

Sepsis in the Severely Neutropenic Host

The approach to the febrile neutropenic patient with possible sepsis has become rather standard, and published guidelines

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are widely available by the Infectious Disease Society of America (IDSA) and similar academic societies worldwide [3, 7•, 8]. These evidence-based guidelines are helpful and well validated, since the management of this group of patients has been particularly well studied in a number of high-quality, systematic, multicenter trials conducted initially by the European Organization of Research in the Treatment of Cancer (EORTC) [9]. More recently, a large number of cooperative oncology study groups throughout the world have published data on the management of sepsis and neutropenia [3, 10, 11]. The widespread acceptance and institution of these guidelines in at-risk patients has markedly reduced the incidence rate and mortality from infectious complications in neutropenic patients. Regrettably, the emergence of multiple antibiotic drug resistant (MDR) pathogens, particularly among gram-negative bacillary organisms, threatens to reverse the gains made in managing patients with prolonged neutropenia [11, 12•]. An up-to-date, evidence-based, set of clinical guidelines for management of sepsis and septic shock is also available in the form of the "surviving sepsis" campaign guidelines [13].

Some definitions and general principles for the management of the neutropenic patient at risk for sepsis include the following (see reference 1 and 12 for detailed review):

1. While neutropenia is technically defined as <1500 neutrophils/mm^3, infection risk is considerably increased at <500 neutrophils/mm^3 and is the accepted cutoff value in most studies of the febrile neutropenia.
2. In immunocompromised patients, fever is defined as an oral or tympanic body temperature of >38 °C (>100.4 °F) that persists for greater than 1 h without an obvious cause (e.g., febrile transfusion reaction, drug fever, etc.) [3].
3. Prolonged neutropenia is defined as ≥7 days and delineates the patient group at greatest risk for infection and sepsis [14].
4. Neutropenic patients often lack the cardinal signs of inflammation making an early diagnosis of infection and sepsis a major challenge [15].
5. Despite the myriad of possible causes and explanations for fever in neutropenic patients, unexplained fever is infection until proven otherwise and antibiotic treatment should be instituted urgently (within 1 h of fever onset if possible) [16].

A general approach to initial decisions regarding empiric antimicrobial therapy should be based upon the following therapeutic principles:

1. Appropriate empiric antimicrobial therapy should be guided by the local susceptibility patterns of pathogens within the health care setting, recent exposure history of the patient to antibiotics, and recent surveillance culture data, if available [3, 16].
2. The primary empiric therapy should target aerobic gram-negative bacilli and consists of monotherapy with broad-spectrum, bactericidal antibiotics such as anti-pseudomonal beta-lactams (cefepime or piperacillin-tazobactam) or carbapenems [3, 17–19], unless clinical circumstances dictate the need for combination antimicrobial therapy (high likelihood of MDR pathogens or presenting in septic shock, in which case combination therapy with addition of fluoroquinolone, aminoglycoside, or colistin might be useful [3, 13].
3. Use dosing strategies to maximize pharmacokinetic and pharmacodynamic principles in order to optimize antimicrobial activity [16].
4. If using a cephalosporin for anti-pseudomonal coverage, add coverage of anaerobic bacteria in patients with evidence of intra-abdominal, necrotizing infections, or culture evidence of anaerobic infection [3].
5. Biomarkers for systemic fungal infections including mannan, beta-D-glucan can be useful in the early detection of invasive candidiasis, and galactomannan assays may be helpful for the diagnosis of invasive aspergillosis, particularly in patients with prolonged neutropenia [3, 13, 16].
6. The initial antibiotic regimen need not cover for possible multidrug resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci as large clinical reviews and meta-analyses in neutropenic patients have not found this approach has significantly improved outcome [20, 21•]. However, their use is warranted if gram-positive infections are known to be present before starting antibiotics or are strongly suspected, such as intravenous catheter infections, cutaneous infections or evidence of streptococcal or staphylococcal toxic shock is present [3].
7. Granulocyte-colony stimulating factor (G-CSF) and other bone marrow growth factors have not convincingly improved overall survival in sepsis associated with febrile neutropenia but can shorten the degree and duration of neutropenia [3]. The potential role of G-CSF as an inducer or contributor to the myeloid reconstitution syndrome (exacerbation or progression of the inflammatory process to a localized infection upon neutrophil recovery) in neutropenic patients is unclear [22].

Careful monitoring and early intervention with appropriate antimicrobials in these vulnerable patients has substantially improved the survival rates in febrile neutropenic patients. A recent study of over 41,000 patients from the United States found that the in-patient mortality associated with febrile neutropenia is now as low as 9.5 % [23]. Even febrile neutropenic patients who develop septic shock have improved survival rates despite the need for critical care [2, 5, 10]. The reduced circulating neutrophil pool in febrile neutropenia may actually

be protective from the generalized endothelial injury characteristically seen in septic shock. Diffuse myeloid cell-endothelial cell adherence and neutrophil-induced proteolytic and oxidant injury are central to the pathophysiology of loss of endothelial barrier function in sepsis [24, 25•]. Neutropenia might limit the endothelial membrane injury in the granulocytopenic patient with severe sepsis/septic shock. Recent advances in early diagnosis of systemic microbial infections using non-culture-based genomic or proteomic systems promise to further improve the outlook for neutropenic patients by allowing specific, directed, antimicrobial therapy to be given early and accurately [26]. A suggested antimicrobial regimen for the initial management of the febrile neutropenic patient is provided in Table 1 [3, 13, 27–29].

Definition of Sepsis and Septic Shock in the Neutropenic Patient

Sepsis was initially defined simply as an infection complicated by a systemic inflammatory response syndrome (SIRS) consisting of fever (or hypothermia), tachycardia, tachypnea, and leukocytosis (or sudden leukopenia) [30]. The term severe sepsis was used to connote a clinical condition of infection+SIRS+evidence of sepsis-induced organ dysfunction. The problem with this set of definitions was that SIRS+infection is a very broad and non-specific set of clinical criteria encompassing essentially any patient with a localized, uncomplicated infection accompanied by fever and leukocytosis. The term "sepsis" lacked the immediate clinical impact that the term should convey to the clinician. Sepsis implies a life-

Table 1 Suggested initial antimicrobial therapy for infection and sepsis in the neutropenic host[a]

Clinical situation	Targeted pathogen(s)	Recommended therapy
At the outset of fever	Enteric and non-fermenting gram-negative bacilli that can be rapidly fatal if untreated in neutropenic patients	Add meropenem 1 g IV every 8 h (or other carbapenem); or piperacillin-tazobactam 4.5 g IV every 6 h; cefepime 2 g IV every 8 h is an alternative[b] (give beta-lactams as slow infusion or as a continuous infusion if possible)
If anaerobic infection suspected	Anaerobic infections associated with intra-abdominal infection, typhlitis, necrotizing soft tissue infections	Add metronidazole 500 mg IV every 8 h; or meropenem (or other carbapenem) 1 g every 8 h
If gram-positive bacterial infection suspected	Soft tissue infections, vascular catheter infections, Gram stain or recent culture evidence of gram-positive bacteria	Add vancomycin 15 mg/kg slowly IV every 12 h until MRSA ruled out; linezolid 600 mg IV every 12 h if vancomycin-intolerant
If fungal infection suspected	In patients with prolonged fever and neutropenia, disseminated candidiasis is main concern; monitor for biomarkers beta-D-glucan for candidiasis and serum galactomannan for aspergillosis and check cultures for other opportunistic fungi such as cryptococcosis and *Fusarium* spp.	Add caspofungin (70 mg IV day 1 and then 50 mg IV daily) or other echinocandin; or voriconazole 6 mg/kg IV every 12 h for day 1 followed by 4 mg/kg IV every 12 h; amphotericin B lipid complex (5 mg/kg IV given daily) or liposomal amphotericin B (3 mg/kg IV given daily) is an alternative for recalcitrant infections and other opportunistic fungal pathogens
If a patient presents in septic shock and if MDR gram-negative pathogens are frequent at your institution[c]	MDR gram-negative pathogens	Start with combination therapy with cefepime or meropenem or piperacillin-tazobactam as recommended in first row and add either a fluoroquinolone or an aminoglycoside plus vancomycin until culture data becomes available; in centers where MDR pathogens with ESBL or carbapenemases (e.g., KPC, NDM-1) are prevalent, addition of empiric therapy with colistin or tigecycline may be considered

MRSA methicillin-resistant *Staphylococcus aureus*, *MDR* multidrug resistant, *ESBL* extended spectrum beta-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *NDM* New Delhi metallo-beta-lactamase

[a] Dosing recommendations are given for a normal-sized adult patient with no significant hepatic or kidney dysfunction or allergy or adverse reaction to the listed antimicrobial agents

[b] Concerns about cefepime safety in neutropenic patients remain. In a meta-analysis, cefepime appeared to worsen outcome as empiric therapy for febrile, neutropenic patients compared to other beta-lactams [27]. A subsequent analysis by the FDA in the United States showed no significant difference in outcomes [28]. A Bayesian analysis by Kalil et al. supported the possible increase in mortality with cefepime-containing regimens [29]. The controversy continues until the present time

[c] In this clinical situation, it is critically important to choose at least one effective agent against the offending pathogen within 1 hour of the diagnosis [3, 14]

threatening, deleterious host response to systemic infection. Calling every infection accompanied by an appropriate host response sepsis makes little sense, confuses the terminology, and greatly overestimates the incidence of sepsis in general medical care [31].

A new proposed definition of sepsis has been developed to clarify the situation and re-acquire the intended meaning of the clinical condition known as sepsis. Sepsis occurs when there is evidence of organ hypoperfusion or dysfunction as a result of a systemic infection. In sepsis, there is a disintegration of cellular communication and function where endothelial and epithelial barrier dysfunction leads to a potentially lethal from of distributive shock with resultant multi-organ dysfunction [32•]. The term "severe sepsis" should be abandoned and replaced by sepsis, as all sepsis is clinically severe. Infection accompanied by an appropriate systemic host response is the definition of infection. The absence of host response to the presence of a microorganism indicates colonization. The term septic shock remains a clinical-pathophysiologic state in which the host response to infection is manifested by acute onset hypotension (operationally defined as a systolic BP< 90 mmHg or mean arterial pressure<65 mmHg) that does not recover with an adequate fluid challenge (>20 ml/kg over 1 hour). This process is often accompanied by multi-organ dysfunction and lactic acidemia (>2 mmol/L) [31, 32•, 33••, 34•, 35•].

The current management of sepsis and septic shock in the immunocompromised patient is very similar to non-immunocompromised hosts and is described in detail in the surviving sepsis campaign guidelines published in 2013 [13]. The basic elements of management include early and aggressive resuscitation to restore circulating blood volume, use of vasopressors as necessary to restore and maintain blood pressure, and early and appropriate use of broad-spectrum, bactericidal antibiotic therapy. Expert supportive care in an intensive care unit (ICU) setting is warranted for monitoring and organ support as needed (e.g., ventilator for acute lung injury, vasopressors for septic shock, hemodialysis for acute kidney injury, blood product support, etc.). A critical element in sepsis therapy is early recognition and initiation of an effective antimicrobial agent as soon as possible. Experimental and clinical evidence indicates that early antibiotics can limit the expansion of the total bacterial load within the host tissues and, therefore, improves chances for patient survival [13, 32•, 36].

In this era of progressive antibiotic resistance development, particularly in gram-negative bacterial pathogens, it critical to choose an initial regimen in patients presenting in septic shock that will cover all possible pathogens. For this reason, combinations of extended spectrum beta-lactams and either a fluoroquinolone or an aminoglycoside is recommended [13]. In regions of the world where MDR pathogens are commonplace and express extended spectrum beta-lactamases and carbapenemases, empiric use of colistin, tigecycline, or fosfomycin can be indicated [11, 12•]. The treatment can be simplified ("de-escalated") to a single active agent once antibiotic susceptibilities are available. One important difference in the supportive care of immunocompromised patients is that experimental therapies that are anti-inflammatory in activity (e.g., high-dose steroids or anti-cytokine therapy) should not be tried in such patients. In fact, immunostimulatory adjuvants might prove to be particularly effective in septic, immunosuppressed patients. Some of these agents include T and B cell growth factors such as interleukin 7, inhibitory antibodies to co-inhibitory signals on antigen presenting cells, or immunostimulatory oligo-deoxynucleotides [37, 38•]. Experimental evidence suggests that these immunostimulators might be effective, but this has yet to be convincingly demonstrated clinically.

Sepsis in Solid Organ Transplant Recipients

Over 30,000 solid organ transplantations are performed every year in the United States, and sepsis remains among the main causes of death among all types of allograft recipients [39]. Nosocomial infections are 18 times more frequent in solid organ transplant (SOT) recipients than in non-transplant patients, which put this patient population at a definite higher risk for developing severe sepsis [6•]. In addition, SOT recipients are 3 times more frequently admitted to hospitals from emergency departments when compared to non-transplant patients [40]. As a general rule, sepsis occurs in 20–60 % of all SOT recipients and is associated with a hospital mortality ranging from 5–40 % [41–46]. Secondly, SOT patients with sepsis do not present with the same classical clinical features seen in non-transplant patients; more specifically, SOT patients tend to have sepsis without leukocytosis and fever, but with more thrombocytopenia and organ failure [6•]. Thirdly, most sepsis episodes affecting SOT recipients are caused by hospital-acquired bacterial infections [6•] and consequently associated with more microbial resistance [44]. In fact, SOT is an independent risk factor for the development of bacteremia due to "ESKAPE" infections (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) [44]. Fourthly, *Candida* spp. is the most common cause of fungemic sepsis in all SOT recipients [47, 48]. And lastly, opportunistic viral infections, in particular cytomegalovirus (CMV), further predispose SOT patients to sepsis [49].

Due to the paucity of specific studies on sepsis and SOT patients, we elected to perform a more inclusive approach by reviewing articles that reported sepsis, severe sepsis, severe bacterial and fungal infections, and bacteremia in transplant recipients. The risk factors for and management of sepsis are highly dependent on the type of allograft; hence, this section

of the manuscript will be divided according to the most common types of transplantation: kidney, liver, heart, and lungs.

Kidney Allograft Recipients

Risk Factors

Risk factors for developing severe infections early after kidney transplantation include anastomotic leaks, contamination of the perfusate or allograft, presence of urinary catheters, ureteral stents, central venous catheters, recent diagnosis of wound infection, and advanced age at the time of transplantation [39]. For infections in the first 6–12 months post-transplant, several risk factors have been observed: vesico-ureteral reflux, female gender, long periods of dialysis before transplantation, diabetes mellitus, polycystic kidney disease, increased aluminum excretion, recurrent UTIs before transplantation, and receipt of deceased donor kidneys [50, 51].

Clinical Presentation

The most common site of infection and source of sepsis in these patients is the urinary tract [52]. Early bacterial infections are related to hematomas, lymphoceles, and anastomotic leaks. These infections may present as UTIs, pyelonephritis, bacteremia, and severe sepsis. The prolonged use venous and urinary catheters, as well as ureteral stents are associated with higher rate of bacterial colonization and nosocomial infections. As an example, the presence of indwelling urinary catheters in kidney recipients raises the incidence of bacteremia to 5–10 % per day [53]. Abdominal ultrasounds should be routinely performed in all kidney recipients with sepsis of urinary source to rule out pyelonephritis, perinephric abscess, fungal balls, and ureteral obstruction; however, other image studies may be necessary in case of high clinical suspicion with a negative ultrasound. If these UTIs become recurrent after renal transplantation, then predisposing factors such as ureteral reflux, uretero-vesicle junction strictures, and neurogenic bladder should be carefully evaluated in order to reduce the recurrence of infections. While sepsis from respiratory source appears to be similar to that from the general population, kidney recipients are more prone to sepsis from abdominal sources such as pericolic abscess and bowel perforation, especially in elderly patients and those with a history of polycystic disease [54–56]. Also, gallbladder stones and pancreatitis are more common in kidney recipients due to the common previous history of hyperparathyroidism and hyperlipidemia associated with chronic renal disease.

Allograft Specific Management

An aggressive evaluation for anatomical complications and foreign bodies as the potential cause of an infection is essential for adequate source control in septic patients. While the general antibiotic management of these patients is similar to non-transplant patients, the duration may vary depending on the extent of infection, source control, and severity of illness. A study that included over 33,000 renal transplantations showed that recipients who required hospitalization due to septicemia had a long-term survival of 9 years (95% CI 7.4–10.6), compared to 15.7 years (95% CI 14.8–16.7) for all other recipients [57].

Liver Allograft Recipients

Risk Factors

Biliary and enteric contamination, poor baseline medical condition, prolonged length of liver transplantation procedure, and extended ICU stay in the post-operative period are all associated with higher risk of infection and sepsis [58, 59]. In addition, pre-transplant conditions such as primary sclerosing cholangitis predispose liver recipients to higher rates of post-operative biliary complications and anastomotic strictures, which increase the risk of sepsis secondary to bacterial cholangitis [60]. Also, the higher the pre-transplant level of bilirubin, the higher the risk of post-op infections [59]. Duct-to-duct biliary anastomosis for biliary drainage is associated with lower rate of infections than roux-en Y choledochojejunostomy [58, 61].

Clinical Presentation

The most common site of infection and source of sepsis in liver recipients is intra-abdominal, and up to 30 % of liver recipients develop bacteremia and sepsis in the first 3 months after transplant [62–64]. Common clinical presentations include intra- or extra-hepatic abscess, secondary peritonitis, cholangitis, which may not present with the classic Charcot's triad and surgical wound infection. In particular, cholangitis may be associated to underlying biliary strictures and intrahepatic abscesses. Procedures such as retrograde cholangiopancreatography and t-tube cholangiography manipulation may lead to ascending cholangitis. The lack of typical cholangitis signs may be confused with graft rejection, so blood cultures and imaging studies can further aid with the differential diagnosis. The differential diagnosis of cholangitis not only includes rejection but also liver ischemia, venous outflow obstruction, and preservation injury [65]. The early post-operative occurrence of peritonitis may suggest the presence of bile leak, and the recurrence of hepatic abscess may indicate the presence of hepatic artery thrombosis, which can lead to graft loss. Imaging studies, such as ultrasounds and CT scans,

should be performed to provide additional clinical information to differentiate between infectious processes, as well as to optimize infection source control. Another potential source of sepsis is *C. difficile* colitis, which is a common infection due to the high use of peri- and post-transplant antibiotics [66•, 67]. Pneumonia is the second most common source of sepsis in liver recipients, which is most common in the first month post-transplantation [59].

Allograft Specific Management

Source control is a crucial part of the treatment of sepsis in liver recipients because of the common association with biliary and vascular anatomical changes. A classic case in point is the diagnosis of hepatic abscess in the presence of hepatic artery thrombosis; this is a complex situation to treat because the poor perfusion precludes of attainment of optimal tissue antibiotic levels, and the common presentation with multiple abscesses precludes adequate drainage. Hence, prolonged therapies and multiple drainages may be necessary, and if these do not work, retransplantation may be the only alternative to eradicate both infection and thrombosis.

Heart Allograft Recipients

Risk Factors

Risk factors associated with sepsis in heart recipients include pre-transplant hospitalization, post-op tracheal intubation for more than 1 day, high-dose steroids, allograft rejection, CMV infection, and post-transplant reintubation [68]. In the first 30–60 days, the infection sources are mostly nosocomial, while the ones occurring from 3–9 months tend to be caused by opportunistic pathogens [69]. A particular fact associated with heart transplantation is related to the common need for multiple devices and foreign bodies before transplantation such as ventricular-assist devices, intra-balloon pumps, pacemakers, automatic implanted cardioverter defibrillators, all of which are known to be associated with chronic and difficult to treat infections. If these devices are infected in the immediate pre-transplant period, the risk of post-transplant mediastinitis and aortic suture infection and dehiscence is elevated [70]. Other infections that may present as sepsis in heart recipients include histoplasmosis, tuberculosis, coccidioidomycosis, strongyloidiasis, and Chagas disease; hence, a detailed geographic residence and travel history is crucial in order to diagnose these infections.

Clinical Presentation

The lungs are the most common source of sepsis in heart recipients, and nosocomial organisms are predominant in the first 2 months post-transplantation. After primary allograft dysfunction, bacterial sepsis is the main cause of death in heart recipients [71]. Most bacteremias and fungemias are nosocomial and associated with mortality up to 30 % [72]. Sternal wound infection and mediastinitis are less frequent but associated with higher morbidity and mortality [72].

Allograft Specific Management

Antibiotics are the mainstream approach to treat sepsis in heart recipients but source control such as sternal wound debridement and drainage of mediastinitis cannot be underscored. Both yeasts and molds are not uncommon causes of sepsis in heart recipients and can have a clinical presentation similar to bacterial sepsis, so fungal infections need to be in the differential diagnosis of sepsis after heart transplantation.

Lung Allograft Recipients

Risk Factors

The denervation of the allograft is associated with impaired mucociliary clearance and reduced cough reflex, while the absence of lymphatic drainage precludes the immune system from quickly reaching the new graft and anastomotic site; all these anatomical changes increase the predisposition for severe infections and sepsis in the post-lung transplantation period. The functional status and previous infectious exposures of the recipient native lungs may have significant consequences in the post-transplantation period. Several risk factors for post-op sepsis have been identified in this patient population including renal failure, morbid obesity, advanced age, malnutrition, diverticular disease, and native lungs of single-lung allograft recipients [73–78]. The presence of bronchiolitis obliterans is associated with an increased risk of pneumonias and decreased long-term survival [74].

Clinical Presentation

Lungs, pleura, and the thoracic cavity are the most common sites of infection leading to sepsis in lung recipients. Because of the direct contact of the allograft with a multitude of different airborne microorganism, these recipients are prone to infections different from other allografts; these include nocardiosis, tuberculosis,

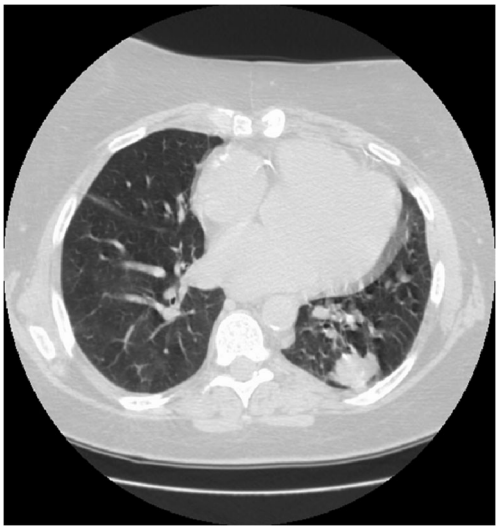

Fig. 1 Computerized axial tomography of the chest in an immunocompromised solid organ transplant patient with pulmonary histoplasmosis

histoplasmosis (See Fig. 1), blastomycosis, coccidioidomycosis, cryptococcosis, aspergillosis, and numerous respiratory viruses that can mimic bacterial pneumonia and sepsis. In particular, *Aspergillus* spp. can cause colonization, tracheobronchitis, sinusitis, and pneumonia. Bacteria are the most common cause of pneumonia and sepsis, but fungal pneumonias are more common in the first 2–3 months post-transplant. Similar to heart recipients, mediastinitis also occurs in lung recipients and can lead to substantial morbidity and mortality mainly in the first month post-transplant [75].

Allograft Specific Management

The diagnosis of a specific respiratory microorganism potentially causing sepsis is crucial for the success of antibiotic therapy in lung transplant recipients. High-quality sputum specimens, mini-bronchoalveolar lavage (BAL) specimens, and BALs can all aid in the identification of these infections. In addition, the visual inspection of the bronchial tree may be helpful in the diagnosis of certain infections; for example, the presence of bronchial pseudomembranes involving anastomotic sites may suggest aspergillosis, while invasive anastomotic infections may suggest candidiasis. Debridement in conjunction with intravenous and inhaled antibiotics and antifungals are all possible ways to treat these infections [76, 77]. Most of the sepsis-related early mortality in lung transplant patients is caused by bacteria, but the mid-late sepsis-related mortality is more commonly associated to mold infections.

Universal Risk Factors

Notably, there are risk factors for post-transplantation sepsis that are common to all types of solid organ transplants:

Table 2 Differential diagnosis of sepsis in solid organ transplant patient

Sepsis mimics in solid organ transplant patients	Distinguishing factors against sepsis
Allograft rejection	Allograft dysfunction, lack of other organ dysfunction
Allograft thrombosis	Sudden allograft dysfunction
Post-transplantation lymphoproliferative disease	Lymphocytosis, EBV viral load increases
Post-operative immediate period	Lack of progressive organ dysfunction
Acute pancreatitis	Absence of infectious source
Cytomegalovirus disease	Presence of CMV DNAemia or positive tissue staining
Pulmonary embolism	Absence of pulmonary consolidations
Myocardial infarction	Predominance of hemodynamic instability without infectious source
Cerebral-vascular accident	Lack of signs of symptoms for meningitis or encephalitis
OKT-3 induced meningitis	Culture and staining negative CSF
Tacrolimus induced pneumonitis	Absence of infectious source
Pulmonary calcinosis	Absence of infectious source
Bronchiolitis obliterans	Pathology findings
Intrathoracic hemorrhage	Bronchoscopy findings
Hypersensitivity drug reaction	Timing with drug administration and presence of rash
Acute respiratory distress syndrome	Progressive hypoxia without infectious source and no development of other organ failure
Acute arterial or venous occlusion	Ischemic findings associated to the affected anatomic area
Acute viral colitis	Presence of viremia or positive tissue staining

(1) CMV serology mismatch, particularly positive donor to negative recipient; (2) the development of CMV disease which itself leads to further immunosuppression and predisposes recipients to higher rates of bacterial and fungal sepsis; (3) prolonged duration of graft cold ischemia; (4) prolonged duration of surgical transplantation procedure; and (5) requirement of large amounts of blood transfusion [39].

Universal Management

Principles of therapeutic management for sepsis that apply to all allograft types include: (1) rapid initiation of intravenous antibiotics with the use of the most optimal dose and administration interval; (2) rapid diagnosis (PCR, antigens, serology, Gram stain, cultures, imaging studies, biopsies); (3) source control: image-guided needle drainage, open surgical drainage, debridement, surgical removal of ischemic or necrotic tissue, removal of infected foreign bodies, such as intravenous and urinary catheters, biliary and ureteral stents, pacemakers and AICD; (4) aggressive search for pathologies that mimic severe sepsis and lead to significant morbidity and mortality if missed (see Table 2); (5) reduction of immunosuppressive drugs to levels that allow better immunological response to fight the infection process, while still preventing graft rejection.

Conclusion

The prevention and treatment of sepsis in the immunocompromised host presents a challenging array of diagnostic and management issues. The neutropenic patient has a primary defect in innate immune responses and is susceptible to conventional and opportunistic pathogens. The solid organ transplant patient has a primary defect in adaptive immunity and is susceptible to a myriad of pathogens that require an effective cellular immune response. Risk for infections in organ transplant recipients is further complicated by mechanical, vascular, and rejection of the transplanted organ itself. The immune suppressed state can modify the cardinal signs of inflammation. Timely diagnostic evaluation and empiric antimicrobial agents can be lifesaving in these patients.

Compliance with Ethics Guidelines

Conflict of Interest Steven Opal reports grants from Arsanis, personal fees from BioAegis, personal fees from Battelle, personal fees from Biocardis, personal fees from Immunexpress, personal fees from Grifolds, grants from Glaxo Smith Kline, grants from Cardeas, grants from Asahi Kasei, personal fees from Elsevier publishers, other from Paratek Pharmaceuticals, other from Achaogen, other from Spectral Diagnostics, outside the submitted work. Andre Kalil reports clinical research grants from Asahi Kasei and Spectral Diagnostics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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