Diagnostic and therapeutic approach to infectious diseases in solid organ transplant recipients

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Abstract

Purpose: Prognosis of solid organ transplant (SOT) recipients has improved, mainly because of better prevention of rejection by immunosuppressive therapies. However, SOT recipients are highly susceptible to conventional and opportunistic infections, which represent a major cause of morbidity, graft dysfunction and mortality.

Methods: Narrative review.

Results: We cover the current epidemiology and main aspects of infections in SOT recipients including risk factors such as postoperative risks and specific risks for different transplant recipients, key points on anti-infective prophylaxis as well as diagnostic and therapeutic approaches. We provide an up-to-date guide for management of the main syndromes that can be encountered in SOT recipients including acute respiratory failure, sepsis or septic shock, and central nervous system infections as well as bacterial infections with multidrug-resistant strains, invasive fungal diseases, viral infections and less common pathogens that may impact this patient population.

Conclusion: We provide state-of-the-art review of available knowledge of critically ill SOT patients with infections.

Keywords: Sepsis, Immunocompromized, Solid organ recipient, Septic shock, Outcome

Introduction

Each year, approximately 90,000 transplants are performed worldwide, more than two-thirds in the USA and Europe, and the number of solid organ transplant (SOT) recipients living with a functioning graft has been growing. In the USA, 19,849, 8000, 3200 and 2449 renal, liver, heart and lung transplants were performed in 2017, respectively (http://www.unos.org/donation). Over the past decades, improvement of graft survival has mainly been attributed to better prevention of acute rejection by immunosuppression therapies. However, these immunocompromised patients are more susceptible to infections caused by both conventional and opportunistic infections, and infection is now the first cause of death of SOT recipients. The diagnosis of infection is often delayed by torpid initial clinical presentation with a secondary and abrupt occurrence of shock and organ dysfunctions. In the present article, we review the main diagnostic and therapeutic approaches to SOT recipients with infections admitted to the ICU.
Epidemiology of severe infections in organ transplant recipients

Infections represent the main cause of death within 1 year after heart or lung transplantation, accounting for 32% and 35% of deaths during this period, respectively. Although with a lesser incidence, infections remain an important cause of death and/or loss of graft survival [1]. The susceptibility of SOT recipients to infections relies on multiple factors including pre-transplant characteristics (i.e., prior immune and non-immune conditions and critical illness), type of transplanted organ, intraoperative characteristics (i.e., prolonged duration of cold ischemia, longer duration of transplant procedure and requirement of blood transfusions) and post-transplant factors (i.e., degree of immunosuppression, prophylaxis and cytomegalovirus infection). Of note, the development of cytomegalovirus infection by itself causes immunosuppression, which further increases the risk of severe bacterial and fungal infections [2, 3]. A timeline of common post-transplant infections has been proposed [4, 5]: severe infections may occur during three classical periods, namely the post-surgical phase (< 4 weeks), the period of maximum immunosuppression (1–12 months) and thereafter (> 12 months) [5] (Fig. 1). Increasing indications of organ transplantation are observed with higher age limits and sicker patients [6], accentuating the incidence of post-transplant infectious complications. Pretransplant critical illness is invariably associated with a higher risk of infection [7] and correlates with the risk of postoperative morbidity and mortality [8]. Approximately 6% of lung transplant recipients in the USA are supported by a ventilator or extracorporeal membrane oxygenation (ECMO) at the time of transplant [9]. Recent studies in heart transplant recipients suggest that 25% of patients had ECMO support at the time of transplant [7, 10].

During the first month after transplantation, infections result from surgical complications, donor-derived infections, preexisting recipient infections and nosocomial infections [11]. The risk is higher for heart, lung and liver transplant recipients compared with kidney transplants. Risk factors that predispose to early postoperative infections (Fig. 2) can be categorized as being present before transplant (recipient or donor) and those secondary to intraoperative or post-transplantation factors [12].

Organ transplantation increases worldwide. The main risk of complication is related to infections, whereas graft rejection risk is now stable. Infectious risk is mainly related to postoperative and nosocomial infections at the early phase. In the intermediate and late phases, opportunistic infections may occur and should be diagnosed early. During the late phase, community-acquired infection risk is common and higher for organ transplant recipients than for immunocompetent patients. Prophylaxis and adapted early preemptive therapy are key to improving global prognosis. ICU admission of infected patients is mainly due to acute respiratory failure, coma and shock. Early diagnostic tests should be oriented toward clinical symptoms, medical history and antimicrobial prophylaxis. Early treatment is key to improve prognosis in solid organ transplant recipients with severe infections.

Take-home messages
Organ transplantation increases worldwide. The main risk of complication is related to infections, whereas graft rejection risk is now stable. Infectious risk is mainly related to postoperative and nosocomial infections at the early phase. In the intermediate and late phases, opportunistic infections may occur and should be diagnosed early. During the late phase, community-acquired infection risk is common and higher for organ transplant recipients than for immunocompetent patients. Prophylaxis and adapted early preemptive therapy are key to improving global prognosis. ICU admission of infected patients is mainly due to acute respiratory failure, coma and shock. Early diagnostic tests should be oriented toward clinical symptoms, medical history and antimicrobial prophylaxis. Early treatment is key to improve prognosis in solid organ transplant recipients with severe infections.

Fig. 1 Timeline of the main severe infections after solid-organ transplantation. a Low incidence in SOT recipients; b highest incidence in lung transplant recipients; c mostly in patients without effective prophylaxis.
Kidney allograft recipient characteristics associated with a higher risk of early postoperative infection include ureteral anastomotic leaks, contaminated perfusate, urinary catheters, ureteral stents and central venous catheters. Risk factors for infection at later time points include vesico-ureteral reflux, polycystic kidney disease, increased albumin excretion and deceased donor kidneys [13]. The most common site of infection is the urinary tract, and abdominal ultrasound is always indicated to identify possible foci for source control such as perinephric abscess, fungal ball or ureteral obstruction. In liver recipients, risk factors are directly related to the allograft anatomy. Pre-transplant conditions such as primary sclerosing cholangitis predispose recipients to postoperative biliary stenosis and anastomotic strictures, both associated with higher risk of bacterial sepsis [14]. The higher the pre-transplant level of bilirubin, the higher the risk of severe infections after transplant. Of note, the Roux-en-Y choledochojunostomy is more frequently associated with biliary infections than the duct-to-duct biliary anastomosis for biliary drainage [15]. Clinical presentation includes acute cholangitis, intra-hepatic or abdominal abscesses, secondary peritonitis and bacteremia. The recurrence of hepatic abscess is suggestive of hepatic artery thrombosis, while the development of peritonitis suggests the presence of biliary leakage. In case of hepatitis C virus (HCV)-positive patients undergoing liver transplantation with detectable HCV viremia, infection of the allograft within hours of organ transplantation as well as recurrent infection is almost universal. HCV recurrence may be prevented by completed direct-acting antiviral therapy before liver transplantation [16] or, if not feasible, started on the day of transplantation until 4 weeks postoperatively [17]. In heart recipients, the pre-transplant need for ventricular-assist devices, intra-balloon pumps, pacemakers and defibrillators is associated with higher risk of post-transplant mediastinitis, aortic suture infections and dehiscence [18]. In lung recipients, the denervation of the allograft is accompanied by a reduced cough reflex and impaired mucociliary clearance, which in turn increase the predisposition to severe pneumonias and sepsis.

Expected donor-derived infections might be caused by CMV [19], Epstein-Barr virus (EBV) and Toxoplasma spp., so preventive strategies are entertained according to the serologic status of the donor and recipient. Unexpected donor-derived infections include *Mycobacterium tuberculosis*, hepatitis B and C viruses [20], West Nile
virus, *Histoplasma* spp. or human immunodeficiency virus [21]. Finally, donor-derived bacterial and/or fungal infections might also be observed [22]. Contamination of the preservation fluid is a rare but sometimes dreadful complication, especially when *Candida* sp. is involved [23].

Infections occurring later (1–12 months after transplant) are mainly due to reactivation of latent infections (cytomegalovirus/CMV, herpes simplex virus/HSV, varicella-zoster virus/VZV) and opportunistic pathogens (*Aspergillus* spp., *Pneumocystis jirovecii*, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Legionella pneumophila*, *Mycobacteria* spp., *Nocardia* spp.).

Infections occurring after 12 months include community-acquired and healthcare-associated infections. *Clostridium difficile* infection is common following transplantation and should be considered in case of diarrhea [24].

Overall, 30–60% of all SOT recipients develop sepsis at any time during the post-transplant period [25–27], mostly nosocomial in the first 2 months, and opportunistic and community-acquired thereafter. SOT recipients are three times more frequently admitted from emergency departments [28] and have 18 times higher risk of developing nosocomial infections [29] compared with non-transplant patients. The fact that SOT recipients are significantly more prone to nosocomial infections makes them also more susceptible to multidrug-resistant (MDR) bacterial infections, including gram-negative bacilli and methicillin-resistant *Staphylococcus aureus* [30]. Acute respiratory failure is the most frequent symptom and is observed in up to 50% of kidney transplant patients requiring ICU admission [31].

In a recent multicenter international study, SOT recipients accounted for 9% of immunocompromised patients admitted to the ICU for acute hypoxemic respiratory failure [32]. Respiratory infection is the most frequent complication after SOT, following a relatively predictable pattern depending on the time elapsed since transplantation [5, 33, 34].

**Assessing the risk of infections in solid organ transplant recipients**

Pretransplant lymphopenia may predict the incidence of infection up to 2 years after liver transplantation [35, 36]. In the post-transplant period, kinetics of lymphocyte subsets are inaccurate predictors of opportunistic infections [37–39]. An immunologic score, the so-called immunoscore, can be computed from immunologic markers, including immunoglobulins, complement levels and lymphocyte subsets readily available in clinical practice. In heart transplant recipients, a high immunoscore was independently associated with an increased risk of severe infection within the next 3 months [37]. However, the receiver-operator characteristic curve (0.80) for predicting infection suggests that the risk of infection not only relies on quantitative depletion of immune effectors but also on qualitative cell dysfunctions (Fig. 3).

Measurement of intracellular ATP levels reflects the metabolic activity of T cells and therefore accounts for a surrogate marker of T cell fitness. Accordingly, low and high ATP levels have been associated with increased risks of infection and rejection, respectively. However, studies that assessed the performance of ATP levels in identifying infection and rejection risks have been conflicting [40]. Very recently, a global immunity assay was

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**Fig. 3** Risk factors for early postoperative infections in SOT recipients. Risk factors that predispose to early postoperative infections in recipients of organ transplantation can be categorized as being present before transplant (recipient or donor) and those secondary to intraoperative or post-transplantation factors.
developed to assess the IFNγ production in whole blood following stimulation of T cells with anti-CD3 antibody and of innate cells with the TLR7 ligand R848. The capacity of IFNγ production was dependent on the type of immunosuppressive regimen and thus was markedly impaired in patients under anti-thymocyte globulin and higher dosing of prednisone and mycophenolate. A low IFNγ production capacity at 1, 3 and 6 months was associated with the development of further bacterial and opportunistic infections [41]. Further works are needed to characterize individual immune function and to assess the relative risk of specific etiologies of infections.

**Key points for anti-infective prophylaxis**
Prophylaxis during the first month following SOT is mainly directed against nosocomial infections related to the donor and surgery. Antibacterial prophylaxis should always take into account the type of transplant as well as colonization of both donor and recipient and should be given for the shortest time possible (Table 1). In case of recipient colonization by an extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae, the prophylaxis should include an antibiotic active against these organisms, sparing carbapenems, if possible [42]. In case of colonization with carbapenemase-producing Enterobacteriaceae (CPE), the risk-benefit ratio may not favor prophylaxis with CPE-active antibiotics, except in centers with a high incidence of surgical site infections [42]. Cystic fibrosis lung transplant recipients frequently harbor MDR bacteria prior to transplantation. These patients should receive early post-transplant prophylaxis based on both donor and recipient bronchial cultures [43].

Prophylaxis has significantly reduced the incidence of opportunistic infections (Table 2) [44, 45]. For CMV prevention, the choice between universal prophylaxis versus preemptive therapy depends on the type of transplant as well as on donor-recipient serology status [46]. After 6 months, in parallel with a progressive reduction in immunosuppression, prophylaxis against opportunistic pathogens can be gradually discontinued. However, prophylaxis should be reinitiated in case of increased immunosuppression to treat rejection episodes.

Of note, severe hypogammaglobulinemia after SOT is associated with CMV, fungal and respiratory infections and with a decrease in the 1-year survival [47, 48]. However, increasing IgG levels to ≥ 400 mg/dl did not translate into better patient or graft survival [47].

**Acute respiratory failure (ARF)**
Respiratory complications after solid organ transplantation (SOT) are frequent, including infectious and non-infectious complications, i.e., lung edema, primary graft dysfunction (PGD), pulmonary hemorrhage or acute respiratory distress syndrome (ARDS) [33]. As the etiology of ARF in SOT recipients is highly variable, appropriate treatment requires timely and accurate diagnosis, the latter being complex because of the effects of immunosuppression, which obscure the signs and symptoms of infection [49]. In some cases, an invasive diagnostic approach is needed to differentiate between infectious and non-infectious causes of ARF (Table 2). Infection may be suspected by laboratory and radiographic abnormalities, but the chest X-ray could be normal in as many as 10% of immunocompromised patients with pneumonia, and evidence may only be present on computed tomography. Lung ultrasound is evolving as an accurate bedside diagnostic tool in critically ill SOT recipients [50–52]. Flexible bronchoscopy is a useful tool in the evaluation of ARF in SOT recipients, and it should be considered early. Microbiologic sampling in bronchoalveolar lavage (BAL), biomarker determination in BAL and plasma (procalcitonin, β-D-glucan and galactomannan) and molecular diagnostic tests are useful to drive the antimicrobial therapy in these patients [49, 51]. Additionally, lung biopsy will be needed to discard graft rejection in lung transplant recipients with overlapping clinical features. Respiratory infections heavily impact the final outcome of SOT, increasing morbidity, including chronic lung allograft dysfunction, and mortality. The emergence of MDR pathogens in post-transplantation infections puts SOT recipients at increased risk of threatening difficult-to-treat complications [50, 51].

**Septic shock**
Some specific features should be taken into account when managing SOT patients with septic shock.

In case of high suspicion of sepsis, onset of broad antibiotic and antifungal therapy is an emergency taking into account specific risk factors for MDR bacteria [53], until identification of the infectious agent and antifungal [54] or antibacterial [55] de-escalation. Non-invasive assays aiming to screen for infections could help to start earlier appropriate antimicrobial therapy [19]. The usefulness of the multiplex panel or next-generation sequencing technologies may be of interest, but these techniques deserve to be validated in SOT recipients. Efforts should be made to find the cause of infection [32], with particular attention to differential diagnoses or a surgical cause that would require surgical revisions [56]. The differential diagnosis of non-infectious complications (i.e., acute allograft rejection or drug-induced toxicity) is complex and may mimic sepsis features [57, 58].
| Pathogen | Risk factors                                                                 | Prophylaxis                                      | Duration  |
|----------|-------------------------------------------------------------------------------|--------------------------------------------------|-----------|
| **Kidney recipients** |                                                                               |                                                  |           |
| Bacteria | *Enterobacteriaceae*                                                          | Prolonged and repeated surgery, technical problems affecting the transplant, vascular and ureteral catheters, undrained collections, urinary leaks, vesico-ureteral reflux | Ciprofloxacin or cefuroxime 48–72 h (keep as short as possible) |
| Fungi    | Pneumocystis jiroveci                                                        | All patients                                     |           |
|          | Candida spp.                                                                  | D+/R−, R+ receiving anti-thymocyte globulin at induction |           |
|          | Aspergillus spp.                                                              | D+/R+                                           |           |
| Viruses  | CMV                                                                           | D+/R−                                           |           |
|          | HSV/IVZV                                                                      | D+/R+                                           |           |
| **Pancreas recipients** |                                                                               |                                                  |           |
| Bacteria | *Enterobacteriaceae, Enterococcus spp., anaerobes, Staphylococcus spp.*       | Prolonged and repeated surgery, technical problems affecting the transplant, vascular catheters, undrained collections, duodenal leaks | Piperacillin–tazobactam + Metronidazole 5–7 days |
| Fungi    | Pneumocystis jiroveci                                                        | All patients                                     |           |
|          | Candida spp.                                                                  | D+/R−                                           |           |
|          | Aspergillus spp.                                                              | D+/R+                                           |           |
| Viruses  | CMV                                                                           | D+/R+                                           |           |
|          | HSV/IVZV                                                                      | D+/R+                                           |           |
| **Intestinal recipients** |                                                                               |                                                  |           |
| Bacteria | *Enterobacteriaceae, Enterococcus spp., anaerobes, Staphylococcus spp.*       | Post-transplant mucositis, prolonged and repeated surgery, technical problems affecting the transplant, vascular and indwelling catheters or tubes, undrained collections, anastomotic leaks | Piperacillin–tazobactam + Metronidazole 4 weeks |
| Fungi    | Pneumocystis jiroveci                                                        | All patients                                     |           |
|          | Candida spp.                                                                  | D+/R−                                           |           |
|          | Aspergillus spp.                                                              | D+/R+                                           |           |
| Viruses  | CMV                                                                           | D+/R+                                           |           |
|          | HSV/IVZV                                                                      | D+/R+                                           |           |
| Pathogen | Risk factors | Prophylaxis | Duration |
|----------|--------------|-------------|----------|
| **Liver recipients** | | | |
| **Bacteria** | Enterobacteriaceae, Enterococcus spp., Staphylococcus spp. | Prolonged and repeated surgery, high number of blood transfusions, technical problems affecting the transplant, vascular catheters, undrained collections, biliary leaks, Roux-en-Y biliary anastomosis | Cefuroxime or Piperacillin-tazobactam | 48–72 h (keep as short as possible) |
| **Fungi** | Pneumocystis jiroveci | High MELD score (> 30), anti-thymocyte globulin, second transplant | TMP–SMX | 3–6 months |
| | Candida spp. | > 2 risk factors: colonization > 3 sites, broad-spectrum antibiotics > 5 days, hemodialysis, second transplant, repeated surgery, high number blood transfusions | Echinocandin followed by Fluconazole | 2–4 weeks |
| | Aspergillus spp. | Colonization, high-dose steroids, allograft dysfunction, second transplant, CMV infection, acute rejection | Aerosolized Amphotericin B, mold activeazole*** | 4–6 weeks |
| **Virus** | CMV | D+ or R+, receiving anti-thymocyte globulin at induction | Valganciclovir* | 3–6 months |
| | HSV, VZV | D+ or R+ | Valacyclovir** | 3 months |
| **Lung recipients** | | | |
| **Bacteria** | Enterobacteriaceae, Pseudomonas spp., Burkholderia spp., Staphylococcus spp. | Prolonged and repeated surgery, technical problems affecting the transplant, vascular and indwelling catheters, undrained collections, bronchial anastomotic leaks | Cefuroxime, adapt to recipient and donor bronchial cultures | 5–7 days |
| **Fungi** | Pneumocystis jiroveci | All patients | TMP–SMX | 12 months, lifelong**** |
| | Aspergillus spp. | All patients or according to risk factors: colonization, high-dose steroids, acute rejection, CMV infection, second transplant | Aerosolized Amphotericin B, Voriconazole | 4–6 weeks, lifelong**** |
| **Viruses** | CMV | D+ or R+ | Valganciclovir | 3–6 months |
| | HSV, VZV | D+ or R+ | Valacyclovir** | 3 months |
| **Heart recipients** | | | |
| **Bacteria** | Enterobacteriaceae, Staphylococcus spp. | Prolonged and repeated surgery, technical problems affecting the transplant, vascular catheters, chest tubes, undrained collections, mediastinal bleeding, anastomotic leaks | Cefuroxime or cefazolin | 48–72 h (keep as short as possible) |
| **Fungi** | Pneumocystis | All patients | TMP–SMX | 12 months |
| | Aspergillus | Colonization, high-dose steroids, second transplant, CMV infection, acute rejection | Aerosolized amphotericin B, voriconazole | 4–6 weeks |
| **Viruses** | CMV | D+ or R+ | Valganciclovir | 3–6 months |
| | HSV, VZV | D+ or R+ | Valacyclovir** | 3 months |
| **Parasites** | Toxoplasma | D+ or R+ | TMP–SMX | Lifelong (D+, R−) or 6 months (R+)|
Drug interactions between immunosuppressive agents (e.g., calcineurin or mammalian target of rapamycin inhibitors) and antibiotics (e.g., rifampicin, macrolides) or azole antifungal treatment should be systematically considered [59] (Fig. 4). Any delay of adequate empiric antibiotic therapy is detrimental, as it is associated with increased mortality in the SOT population [60, 61].

There is no consensus on the management of immunosuppressive drugs in critically ill patients with sepsis [62]. Some authors suggest withdrawing immunosuppressive drugs to accelerate sepsis recovery [63]. However, the benefit of this strategy has not been proven yet and may expose the patient to the risk of allograft rejection [64]. Hydrocortisone should be considered in all septic SOT recipients on corticosteroids before ICU admission to avoid adrenal insufficiency [65]. Concerning the choice of fluids, crystalloids should be used as first-line, while colloids such as hydroxyethyl starches, when used in deceased organ donors, have been associated with delayed graft function in kidney transplant recipients [66]. Use of vasopressors should also follow current guidelines, where norepinephrine is proposed as the drug of choice [67]. Inotropic drugs should be considered in those who fail to respond to adequate fluids and vasopressors and also have myocardial depression [67]. However, the response to vasopressors may be modified in SOT recipients. For example, some authors have suggested that sympathetic denervation in kidney transplants may increase the effect of norepinephrine on renal vascular resistance [68]. The response to inotropic drugs may also be decreased in heart transplant recipients [68].

**CNS infections in SOT recipients**

In patients receiving chronic immunosuppressive therapy after solid organ transplantation (SOT), central nervous system (CNS) opportunistic infections typically occur within 6–12 months following transplantation [69, 70]. A general diagnostic approach to neurologic complications of SOT is proposed elsewhere [71]. Main diagnostic studies for SOT patients with a suspicion of CNS infection are presented in Table 3.

Fungi are a frequent cause of cerebral abscesses among SOT recipients, e.g., resulting from infection by *Aspergillus*, *Mucorales*, *Scedosporium* or *Fusarium* species [72, 73]. *Aspergillus* sp. may also be responsible for ischemic and hemorrhagic brain lesions [74]. Voriconazole is the standard treatment for CNS aspergillosis but requires therapeutic drug monitoring to optimize therapy and avoid toxicity (optimal trough concentrations of 2–5 μg per ml in serum). Voriconazole has a 50% penetration coefficient in the CNS, and measurement of CSF concentrations is not necessary in routine. For patients experiencing severe adverse effects under voriconazole as
primary therapy, liposomal amphotericin B is an alternative. Monitoring of the therapeutic response in patients with altered mental status should be based on serial CT or MR scans with an initial interval of 1 to 2 weeks. Neurosurgery should be consulted for any patient presenting with a suspicion of CNS aspergillosis or other mold infection. In the absence of extra-CNS involvement (i.e., a pulmonary or sinus source of infection), a definitive diagnosis requires brain biopsy, with prompt inspection of the specimen. In patients presenting with space-occupying lesions or hydrocephalus, surgical decompression [with debulking or stereotactic drainage of lesion(s)] and insertion of an extraventricular drainage catheter should be discussed, respectively.

Other common microbial isolates in brain abscesses of SOT recipients include *Nocardia* species, *Toxoplasma gondii* and *Mycobacterium tuberculosis*. Nocardiosis is more frequent after thoracic transplantation and prolonged ICU stay in case of an intense immunosuppressive regimen (high calcineurin inhibitor trough concentration, high-dose steroids) and/or use of tacrolimus [75]. More than 40% of patients have a disseminated infection, including lung and cutaneous involvement. CNS involvement occurs in one-third of patients and can be asymptomatic, suggesting that systematic brain imaging is mandatory at diagnosis. Cotrimoxazole is the drug of choice, but other drugs such as linezolid, carbapenems and amikacin have been proposed [76]. The most common presentation of *Toxoplasma gondii* infection in SOT recipients is primary infection with (multi-)organ disease (i.e., retinochoroiditis, pneumonia, myocardial involvement) with or without neurologic features, i.e., meningitis and/or (multi-)focal brain lesions [77]. A negative serostatus prior to transplantation represents the only risk factor associated with the disease [78]. In most patients, the diagnosis will be made by means of specific (CSF) PCR. Myocardial involvement is associated with poor outcome.

The incidence of bacterial meningitis is seven-fold higher compared with the general population, and causative pathogens include *Streptococcus pneumoniae* and gram-negative bacilli [79]. Cryptococcosis is a rare and severe complication of SOT, especially in lung transplant recipients, with CNS involvement being observed in 50% of cases [80]. Tuberculous meningitis has also been reported in SOT [81], but its exact incidence is unknown. HSV and VZV are common viruses causing encephalitis in immunocompromised individuals, although clinical manifestations may be atypical (i.e., absence of fever, absence of CSF pleocytosis, atypical MRI patterns) and thus challenging to recognize [82]. In the setting of SOT, donor-transmitted infections can result in rare causes of

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**Table 2 Non-invasive and invasive diagnostic tools for acute respiratory failure in SOT recipients**

| Diagnostic tool                              | Diagnostic usefulness                                                                                                                                                                                                 |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chest radiography and lung tomography        | Radiographic appearance of pulmonary infiltrates  
Bacterial infection or pulmonary hemorrhage  
Bronchopneumonia and peribronchial opacity: respiratory viruses, mycobacteria, *Mycoplasma*, *Chlamydia*, *Neisseria*, *Haemophilus* spp.  
Diffuse interstitial infiltrates: infection (*Pneumocystis jiroveci*), respiratory viruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, graft rejection, lung edema, pulmonary hemorrhage, ARDSa  
Nodular infiltrates: bacteria, *Aspergillus* spp.                                                                 |
| Lung ultrasound                               | Ultrasound patterns  
Consolidation: pneumonia, atelectasis  
Interstitial syndrome: infection, graft rejection, lung edema, pulmonary hemorrhage, ARDSa                                                                 |
| Biomarkers                                    | Rejection: circulating anti-HLA antibodies  
Infection: Procalcitonin, c-reactive protein  
Specific blood tests: galactomannan, β-d-glucan, specific PCRb for viruses, bacteria, parasites and fungi                                                                 |
| Flexible bronchoscopy BALc                   | Microbiologic identification by culture or molecular techniques of lung infection  
Pulmonary hemorrhage  
Galactomannan for invasive Aspergillosis                                                                 |
| Flexible bronchoscopy trans-bronchial biopsy | Graft rejection: mononuclear inflammatory cell infiltrates centered around small vessels and capillaries and/or small airways  
Invasive aspergillosis: septate, acute branching hyphae |

a ARDS Acute respiratory distress syndrome  
b PCR Polymerase chain reaction  
c BAL Bronchoalveolar lavage
Table 3 Main diagnostic studies of SOT patients with a suspicion of CNS infections

| Pathogen                               | Clinical picture                                      | CSF findings                          | Brain imaging                      | CSF samples | Blood samples | Other samples               |
|----------------------------------------|-------------------------------------------------------|---------------------------------------|------------------------------------|-------------|---------------|-----------------------------|
| **Bacteria**                           |                                                       |                                       |                                    |             |               |                             |
| *Streptococcus pneumonia*              | Acute onset                                          | Pleocytosis (100–10,000/mm³) Neutrophils High Pt; Low Glu | Normal or infarction Diffuse edema | Direct examination and culture (± 16 s RNA) mPCR  | Blood cultures | Depending on clinical presentation |
| *Neisseria meningitidis*               | Acute onset                                          | Pleocytosis (100–1,000/mm³) Lymphocytes High Pt; Low Glu | Arachnoiditis Infarction Hydrocephalus Tuberculoma | Direct and culture (3–5 ml, repeat CSF analysis) QuantIFERON-TB | PCR for *Mycobacterium tuberculosis* complex | Pulmonary samples Brain biopsy |
| *Gram-negative bacilli*                | Subacute onset                                        | Pleocytosis (> 5/mm³) Lymphocytes High Pt; Normal Glu | Ischemic lesions                   | PCR HSV1 and HSV2 PCR HSV1 and HSV2 | –             |                             |
| *Listeria monocytogenes*               | Subacute onset                                        | Pleocytosis (> 5/mm³) Lymphocytes High Pt; Normal Glu | Ischemic lesions                   | PCR HSV1 and HSV2 | –             |                             |
| **Viruses**                            |                                                       |                                       |                                    |             |               |                             |
| *Herpes simplex virus*                 | Acute onset of altered mental status ± focal signs, ± fever, ± seizures | Pleocytosis (> 5/mm³) Lymphocytes High Pt; Normal Glu | Temporal lesion(s)                 | PCR HSV1 and HSV2 PCR HSV1 and HSV2 | –             |                             |
| *Varicella zoster virus*               | Acute onset of altered mental status ± focal signs, ± fever, ± seizures | Pleocytosis (> 5/mm³) Lymphocytes High Pt; Normal Glu | Ischemic lesions                   | PCR VZV PCR VZV | Skin biopsy (PCR)          |                             |
| *Cytomegalovirus*                      | Subacute onset of altered mental status ± fever       | Pleocytosis (> 5/mm³) Lymphocytes High Pt; Normal Glu | Venticulitis                        | PCR CMV PCR CMV | –             |                             |
| **JC virus**                           | Subacute onset of altered mental status ± focal signs ± seizures | Absence of pleocytosis Multifocal white matter lesions | PCR JC virus                       | –           | –             |                             |
| **HHV6**                               | Sub-acute onset of altered mental status              | Pleocytosis (> 5/mm³) Lymphocytes High Pt; Normal Glu | Limbic lesions                     | PCR HHV6 | –             | –                           |
| **Epstein-Barr virus**                 | Focal signs                                          | –                                     | Focal lesion                        | PCR EBV | Brain biopsy if focal mass (look for lymphoma) |                             |
| **Parasites and fungi**                |                                                       |                                       |                                    |             |               |                             |
| *Aspergillus and other molds*          | Focal deficits ± extra neurologic involvement         | Variable                             | Cerebral infarcts Hemorrhage Mycotic aneurysm Abscesses + + | Direct examination and fungal cultures Galactomannan 1-3-β-D-glucan | Galactomannan | Pulmonary samples Skin biopsy Brain biopsy |
| *Toxoplasma gondii*                    | Altered mental status ± fever ± seizure               | Abscess(es)                          | PCR Toxoplasma gondii              | PCR Toxoplasma gondii | PCR | Pulmonary samples + brain biopsy |
encephalitis, including infection by human herpes virus-6 and BK virus. Progressive multifocal leukoencephalopathy (PML) has been reported in SOT recipients, with a higher case fatality rate and a higher incidence than reported in human immunodeficiency virus patients or multiple sclerosis patients treated with natalizumab [83]. Future studies using multiplex CSF PCR and next-generation sequencing techniques may allow a faster diagnosis and help identify new pathogens, respectively.

**Impact of multidrug-resistant (MDR) bacteria on the risk of severe infections in SOT recipients**

SOT recipients represent a particular setting of patients at risk of developing MDR infections, as they are frequently and broadly exposed to multiple antibiotic courses, invasive procedures, immunosuppressive treatments and have repeated contacts with healthcare structures—all of them highly recognized and proven risk factors for MDR bacterial infections [84]. No specific recommendations about prevention and treatment in this setting are currently available.

Transplant recipients are exposed to risk developing hospital- and healthcare-associated infections, especially in the early post-transplant period. SOT recipients are typically infected by non-fermenting gram-negative bacilli (i.e., *Pseudomonas aeruginosa*, *Burkholderia* spp., *Stenotrophomonas* spp. or carbapenem-resistant *Acinetobacter baumannii*), extended-spectrum β-lactamases (ESBL) and carbapenem-resistant enterobacteriaceae (CRE), especially carbapenem-resistant *Klebsiella*
Invasive fungal infections

Invasive fungal disease (IFD) is associated with morbidity, reduced graft survival and mortality in SOT recipients. The risk and type of IFD mainly depend on the type of transplant. Invasive aspergillosis is the most frequent IFD, occurring mostly in the first year after transplant. Invasive aspergillosis (IA) represents 25% (except for lung transplant, 59%) and cryptococcosis 7% of IFD in SOT recipients [90]. Mold infections occur after the first year especially in lung transplants, but earlier onset infections have been reported in liver transplant recipients presenting more frequently with disseminated disease (55%) [91]. Preventive measures and diagnostic strategies for IFD therefore depend on the type of organ transplanted and associated risk factors and are presented in Table 4.

Donor-derived infections occur mostly within 30 days post-transplant. Candida vascular infections due to preservation fluid contamination are mostly reported for kidney and liver transplants [23, 92]. Graft-transmitted cryptococcosis, coccidioidomycosis and aspergillosis have also been reported [93, 94]. SOT recipients treated for IFD are also at risk to develop immune reconstitution syndrome (IRS) after immunosuppression tapering. It is classically reported in cryptococcosis [95] but also in histoplasmosis. IRS is reported in 15% of SOT patients developing cryptococcosis. Risk factors include CNS disease and discontinuation of calcineurin inhibitors [96]. IRS is associated with more graft rejection. IRS treatment mainly includes corticosteroids and, in rare cases, TNF-alpha inhibitors [97].

Invasive candidiasis represents 50–60% IFD in SOT recipients. They are mostly bloodstream infections (44%), followed by intra-abdominal (14%), and occur mostly in liver (41%) and kidney (35%) transplant. Mortality is higher in liver transplant [98]. Diagnosis relies on blood cultures and treatment with echinocandins or fluconazole in non-severe, non-azole pre-exposed patients.

Aspergillosis incidence is high in lung and heart transplant recipients (8.3 and 7.1% in the Swiss cohort) [90]. Diagnosis relies on CT scans [that show images of angioinvasive invasive pulmonary aspergillosis (IPA) in only half of patients], respiratory specimen assays including direct examination (49%), culture (70%) and galactomannan assay (GM) positivity in blood (35%) or BAL (39%). Serum beta-1,3-glucan had a poor positive predictive value of 27% in a cohort of SOT recipients (mostly lung) for IFI [99]. Two studies showed the importance of voriconazole for IA treatment in both kidney and liver transplant recipients with demonstrated reduced mortality [100, 101].

Pneumocystis pneumonia mostly occurs 2 years post-transplant because of universal prophylaxis during the first year. It is associated with age, total lymphocyte count and CMV infection [102–104]. Clinical presentation may be severe with a 40% rate of ICU admission [103]. Use of corticosteroids in SOT recipients with pneumocystis pneumonia is a matter of debate.

Viral infections

Viral infections in SOT recipients may be divided into opportunistic infections and common respiratory viral infections. Opportunistic viral infections are mainly due to herpesviridae, CMV being the most frequently
| Most typical clinical setting, including main risk factors | Fever with no respiratory signs or symptoms | Nodular* lung lesions ± fever (may be absent in case of steroid therapy) | Ground-glass opacities (and exertional dyspnea) ± fever | Rhino-sino-orbital infection, with possible brain involvement |
|----------------------------------------------------------|--------------------------------------------|---------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------|
| Early after SOT, Liver, small bowel, pancreas transplant, Reoperation and re-transplantation, Antibiotic administration, Dialysis | Lung* or heart transplant, Early after SOT in case of heart and liver, later in case of lung (particularly if mold-active prophylaxis is administered), Rejection, Other infections | Late after SOT, Kidney transplant, Absence of PjP prophylaxis, Lymphopenia, Rejection | Late after SOT, Kidney transplant, Absence of PjP prophylaxis, Lymphopenia, Rejection |
| Main fungal pathogens to suspect | Candida | Aspergillus | Pneumocystis | Mucorales |
| Other rare pathogens to consider | Cryptococcus (late after SOT, particularly in renal tpx; possible disseminated also to CNS), Histoplasma (very rare < 1%; endemic areas, community outbreaks) | Consider other molds (Mucorales, Fusarium), Cryptococcus (see left), Histoplasma (see left; frequently disseminated) | Aspecific presentation of other IFD, usually other types of lung lesions coexist | Aspergillus |
| Main diagnostic tests | Blood culture, Culture of recently placed abdominal drain in case of abdominal candidiasis | BAL with direct microscopy, culture and GM | PCR or microscopy in BAL | Histologic exam and culture of biopsy |
| Other useful tests | 1,3-Beta-d-glucan, PCR | PCR in BAL, Serum GM | Serum BDG (NPV > 95%), PCR | |
| Treatment | Echinocandin for non-albicans and azoles for albicans, Alternative: l-AmB, Azoles (mainly for step-down) | Voriconazole, Isavuconazole (potentially fewer drug interactions and side effects but short experience), l-AmB | TMP/SMX, Alternatives (in case of severe allergy): Clindamycin + primaquine, Pentamidine IV, Atovaquone PO, l-AmB, Isavuconazole, Alternative: Posaconazole | l-AmB, Isavuconazole, Alternative: Posaconazole, AND surgical debridement |
| Length of treatment | For candidemia 14 days after the first negative blood culture | At least 1 2 weeks | 3 weeks, secondary prophylaxis usually warranted | Individualized, at least 12 weeks |

BDG beta- 1,3-d-glucan, GM galactomannan, l-AmB liposomal amphotericin B, NPV negative predictive value, PjP Pneumocystis jirovecii pneumonia, SMX sulfamethoxazole, TMP trimethoprim  

* Angio-invasive lesions, such as nodules and cavitations, are more typical for neutropenic patients, while other patients may have less typical, aspecific lesions due to the airway-invasive pattern of mold infection (micronodular, peribronchial or even consolidations or ground-glass)  

† Tracheobronchitis or infection of bronchial anastomosis may occur; Aspergillus colonizations in the lungs or sinuses are important risk factors.
encountered. Typically, CMV infection (defined as evidence of CMV replication regardless of symptoms [46]) occurs in the first 3 months regardless of symptoms of SOT recipients [110, 111], leading in some cases to chronic lung allograft dysfunction [112]. Moreover, it seems that viral-bacterial and/or fungal co-infection is more common than in immunocompetent individuals and that viral shedding is longer in SOT recipients than in immunocompetent patients [111]. Although antiviral treatments are limited and the timing of their administration is not clearly defined, all SOT recipients with suspected respiratory infection should be sampled (nasopharyngeal sample or deep lung if mechanically ventilated) to test for these viruses (including influenza) by PCR. Treatment is mainly supportive, but also includes specific antiviral treatment, if available, and reduction of immunosuppression [113]. Empiric oseltamivir should be given in all respiratory infections as early as possible during the flu period in SOT recipients and continued or withdrawn according to PCR results. In case of severe influenza, lung transplant recipients and other particularly severely immunosuppressed SOT recipients (i.e., having recently received anti-rejection therapy and/or anti-thymocytes globulins) should receive a combination therapy including oral oseltamivir and baloxavir. There is no evidence that a double dose of oseltamivir is superior to a single dose; therefore, 75 mg twice daily is recommended for all patients. If oral therapy is impossible, intravenous peramivir is an option. Inhaled zanamivir has not been evaluated in patients with severe influenza and in SOT patients (in particular lung transplant recipients) and could therefore not be recommended for routine use. Intravenous zanamivir may be another alternative, in particular in case of oseltamivir-resistant influenza infections, but is only available for compassionate use. Duration of therapy should depend on therapeutic response and respiratory viral loads measured by PCR: oseltamivir can be stopped after 5 days if there is clinical improvement and virus is no longer detected, but should be continued for 10 days in all other cases, in particular for severe influenza.

**Uncommon pathogens that should be known**

Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment and stand out as the most important uncommon pathogens in SOT recipients. Among them, *Mycobacterium avium* and *M. intracellulare* [commonly referred as *Mycobacterium avium complex (MAC)*] are the most common NTM species causing disease in SOT recipients [114]. Less commonly encountered NTMs include the slow-growing *M. kansasi*, *M. haemophilum* and *M. marinum* and the rapid-growing *M. fortuitum*, *M. chelonea* and *M. abscessus*. The lung is affected in > 50% of cases, with heart and lung recipients being more vulnerable (range from 0.2 to 2.8% and 0.5 to
8.0%, respectively) compared with kidney (range 0.16 to 0.38%) and liver recipients (0.04%). The median onset is $\geq 1$ year post-transplantation, later than tuberculosis [114]. Chronic cough, sputum production and hemoptysis are common in lung infection, whereas disseminated disease (fever, night sweats, etc.) and cutaneous infection are rarer with MAC. Rapidly growing mycobacteria usually cause limited cutaneous disease; M. abscessus and M. chelonae may cause more severe and disseminated diseases [115]. NTM should be suspected in SOT recipients with pulmonary symptoms, particularly lung transplant recipients with chronic allograft dysfunction; all bronchoscopy specimens and all atypical skin lesions should be biopsied, stained and cultured for acid-fast bacilli. Radiology features overlap with many other diseases and TB [114]. NTM-associated mortality is generally low, but large studies are scarce. Infections caused by M. abscessus have worse outcomes, particularly in lung transplant recipients, and pre-transplant colonization is considered a contra-indication to lung transplantation by some transplant centers. NTM infections in lung recipients are associated with increased mortality and poor allograft function despite control of the infection [116]. Treatment may be challenged by interactions of rifamycins and clarithromycin, both significant components of NTM treatment regimens, with the calcineurin inhibitors and rapamycin [114]. As mentioned above for fungal infections, lowering of the dose of immunosuppressants may trigger IRS with all mycobacterial infections [7].

Endemic fungi (Histoplasma capsulatum, Coccioidioides spp., Paracoccidioides spp., Blastomyces dermatitidis, Cryptococcus gattii) cause disease in geographically specified areas, whereas other pathogens common in the environment, such as Cryptococcus neoformans, Aspergillus spp. and Cryptosporidia spp., have worldwide distribution. Clinical features, severity and duration of infection may vary significantly compared with normal hosts or other groups of immunosuppressed hosts (i.e., HIV patients) [31, 117]. Lymphocytic choriomeningitis virus (LCMV), rabies virus, Leishmania spp., Trypanosoma cruzi (causing Chagas disease), Balamuthia mandrillaris, Eucalyptozyoon cuniculi (causing microsporidiosis), Strongyloides stercoralis, Echinococcus granulosus, Filarias spp., Schistosoma spp. and Plasmodium spp. can cause donor-derived infections [31, 117, 118]. Most of these infections can present with an aggravated or non-typical course because of immunosuppression, and mortality varies depending on the pathogen, depth of immunosuppression and rapidity of diagnosis. LCMV was transmitted to all organ transplant recipients causing death in seven of eight recipients from the same donor in one report [31]. Most of the above-mentioned pathogens cause geographically restricted infections; therefore, strict screening protocols have to be applied to the donor and/or the recipient, according to their anticipated local exposure to unusual pathogens [119].

**Conclusion**

Infection in SOT recipients is a frequent cause of admission in the ICU and is associated with both morbidity and mortality. Early diagnostic approaches are required to improve the prognosis. The diagnostic approaches should combine available knowledge on postoperative infections and profound immune suppression at the early phase, established immunocompromised status in the intermediate phase, and both community and opportunistic infections at the late phase. The empirical therapy should be decided early according to epidemiology, clinical presentation and emergent diagnostic procedures taking into account possible toxicity, pharmacokinetics and interactions with immunosuppressive therapy.

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**Compliance with ethical standards**

MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Biomerieux, CIDara, Gilead, Menarini, MSD, Nabirva, Paratek, Pfizer, Roche, The Medicine
Company, Shionogi, Tetraphase, VenatoRx and Vfor. RF reports participation in scientific advisory boards: MSD, Shionogi and lectures: Beckton-Dickinson, MSD, Astellas, Pfizer, Thermo, Estor. SJ reports receiving consulting fees from Drager, Hamilton, Maquet, Medtronic and Fisher & Paykel. CEL reports participations in advisory boards (Bayer Healthcare, Carmaq, Farcon, ThermoFischer Brahms) and lectures (MSD, Nihon-Koden, Biomerieux). MM has received payment for lectures, advisory board participation and travel expenses from MSD, Jansen, Pfizer, Astelas, Gilead, all outside the submitted work. FP reports personal fees from MSD, Gilead, Jansen, Pfizer, Astelas, Gilead, all outside the submitted work. CV has served on scientific advisory boards (AstraZeneca, Pfizer, MSD, Nabriva, Gilead), lectures (Biomérieux, MSD, Astellas, Pfizer) and scientific grants (MSD, Pfizer). CV reports personal fees from MSD Int, Gilead, Pfizer, Angelini, Astelas and Basilea. LZ reports scientific grants not related to the review by Jazz Pharmaceuticals.

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References
1. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AV, Levine BJ, Meiser B, Rossano JW, Chambers DC, Yusen RD, Stelhik J (2017) The registry of the international society for heart and lung transplantation: thirty-fourth adult heart transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant Off Publ Int Soc Heart Transplant 36:1037–1046
2. Kall AC, Levitsky J, Lyden E, Stoner J, Freifeld AG (2005) Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med 143:870–880
3. Kall AC, Dikroub H, Freifeld AG (2007) Sepsis and solid organ transplantation. Curr Drug Targets 8:533–541
4. Fishman JA, Rubin RH (1998) Infection in organ-transplant recipients. N Engl J Med 338:1741–1751
5. Fishman JA (2017) Infection in organ transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 17:896–879
6. Poole D, Skrzak S, Mehra MR (2018) Prediction of optimal outcomes in organ transplantation. Intensive Care Med. https://doi.org/10.1007/s00134-018-5472-6
7. Pons S, Sonneville R, Bouadma L, Styfalova L, Ruckly S, Neuville M, Radou J, Lebut J, Dilly MP, Mourvillier B, Dorent R, Nataf P, Wolff M, Timsit JF (2019) Infectious complications following heart transplantation in the first month of solid organ transplantation. Transpl Infect Dis Off J Int Transplant Soc 11:2674–2682
8. Valapour M, Lehr CJ, Skeans MA, Smith JM, Carrico R, Uccellini K, Arshad S, Jeepalyam S, Bruni S, Miceli M, Jacobsen U, Salluh J, Schellongowski P, Rusinova K, Terzi N, Mehta S, Antonelli M, Hemelaar P, Lemiale V, Taccone FS, Martin Loeches I, Meyhoff TS, A, Hemelaar P, Lemiale V, Taccone FS, Martin Loeches I, Meyhoff TS (2017) Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med 376:2394–2395
9. Ison MG, Hager J, Blumberg J, Durick J, Carney K, Curter J, Dimajo JM, Hasz R, Kuehnert MJ, Orito R, Teperman L, Nalesnik M (2009) Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant 9:1929–1935
10. Mularoni A, Berti A, Vizzini G, Gona F, Campanella M, Spada M, Grut-tadaria S, Vitulo P, Conaldi P, Luca A, Gridelli B, Grossi P (2015) Outcome of transplantation using organs from donors infected or colonized with carbapenem-resistant gram-negative bacteria. Am J Transplant 15:2674–2682
11. Levitskev E, Suet G, Meric J, Compagnon P, Amathieu R, Feser C, Botteriel F, Foulou F, Azoulay D, Honnere G (2014) Candida vascular complication in a liver transplant recipient due to yeast contamination of preservation solution. Transplant Infect Dis Off J Transplant Soc 16:827–829
12. Mittal C, Hassan S, Arshid S, Jeppeyam S, Bruni S, Miloch M, Jacobsen G, Abouljoud M, Bajjoka I, Ramesh M, Alangaden G (2014) Clostridium difficile infection in liver transplant recipients: a retrospective study of rates, risk factors and outcomes. Am J Transplant 14:1901–1907
13. Hsue RB, Chang CJ, Fang CT, Chang SC, Wang SS, Chu SH (2011) Bloodstream infection in heart transplant recipients. 12-year experience at a university hospital in Taiwan. Eur J Cardiothorac Surg 40:1362–1367
14. Wang Y, Q Z, Zhou J (2013) Mortality predictors of bloodstream infections in solid-organ transplant recipients. Exp Clin Transplant 11:211–214
15. Florescu DF, Sandkovskiy U, Kall AC (2017) Sepsis and challenging infections in the immunosuppressed patient in the intensive care unit. Infect Dis Clin N Am 31:415–434
16. Trzeciak S, Shacer R, Pipper D, Chan T, Kessler C, Dellinger RP, Pursell KJ (2004) Infections and severe sepsis in solid-organ transplant patients admitted from a university-based ED. Am J Emerg Med 22:530–533
17. Kall AC, Syed A, Rupp ME, Chambers H, Vargas L, Maskin A, Miles CD, Langnas A, Florescu DF (2015) Is bacteremic sepsis associated with higher mortality in transplant recipients than in nontransplant patients? A matched case-control propensity-adjusted study. Clin Infect Dis Off Publ Infect Dis Soc Am 60:216–222
18. Bodro M, Sabe N, Tubau F, Liado L, Ballellas C, Roza J, Cruzado JM, Caratala J (2011) Risk factors and outcomes of bacteremia caused by drug-resistant ESKEAPE pathogens in solid-organ transplant recipients. Transplantation 96:843–849
19. Canet E, Zafriani L, Azoolay E (2016) The critically ill kidney transplant recipient: a narrative review. Chest 149:1546–1553
20. Azoolay E, Pickers P, Soares M, Perner A, Rello J, Bauer PR, van de Loouw A, Hemelaar P, Nemoto M, Vilacon R, Hochendel A, Meyhoff TS, Sallhub J, Schellongowski P, Ruisvina K, Terzi N, Mehta S, Antonelli M, Koutachet A, Bireutt D, Valkonen M, Landberg PB, Brunel B, Bukari RB, Pere F, Metaxa V, Moreau AS, Suenouv V, Burghi G, Girault C, Silva
33. Kotloff RM, Ahya VN, Crawford SW (2004) Pulmonary complications of solid organ and hematopoietic stem cell transplantation. Am J Respir Crit Care Med 170:22–48

35. Fernandez-Ruiz M, Lopez-Medrano F, Allende LM, Meneu JC, Fundora-Suarez Y, San-Juan R, Lizardoan M, Paz-Artal E, Aguado JM (2009) Peritransplant lymphocyte count predicts the incidence of infection after the first two years after liver transplantation. Liver Transpl 15:1209–1216

36. Nierenberg NE, Poutsiaka DD, Chow JK, Cooper J, Price LL, Freeman RB, Rohrer R, Snyderman DR (2014) Peritransplant lymphopenia is a novel prognostic factor in cytomegalovirus and noncytomegalovirus infections after liver transplantation. Liver Transpl 20:1497–1507

37. Sarmiento E, Navarro J, Fernandez-Yanez J, Palomo J, Munoz P, Carbone RB, Rohrer R, Snydman DR (2014) Pretransplant lymphopenia is a novel marker of severe infection in heart recipients. Transplant Infect Dis 16:802–812

38. Calastra SA, Zelini P, De Silvestri A, Chesa A, Comolli G, Sacchi M, Gigotto C, Pellegrini C, Esposito P, Minoli L, Tinelli C, Marone P, Baldanti F (2012) Kinetics of lymphocyte subsets and posttransplant opportunistic infections in heart and kidney transplant recipients. Transplantation 93:112–119

39. Fernandez-Ruiz M, Lopez-Medrano F, Allende LM, Andres A, Garcia-Reyne A, Lumbresas C, San-Juan R, Morales JM, Paz-Artal E, Aguado JM (2014) Kinetics of peripheral blood lymphocyte subpopulations predicts the occurrence of opportunistic infection after kidney transplantation. Transpl Int 27:67–685

40. Ling X, Xiong J, Liang W, Schroder PM, Wu L, Ju W, Kong Y, Shang Y, Guo Z, He X (2012) Can immune cell function assay identify patients at risk of infection or rejection? A meta-analysis. Transplantation 93:737–743

41. Mian M, Natori Y, Ferreira V, Selzner N, Husain S, Singer L, Kim SJ, Yozu Z, He X (2012) Can immune cell function assay identify patients at risk of infection or rejection? A meta-analysis. Transplantation 93:737–743

42. Aguado JM, Silva JT, Fernandez-Ruiz M, Cordero E, Fortun J, Gudiol C, Martinez-Martinez L, Vidal E, Almenar L, Almirante B, Canton R, Carratala J, Caston JJ, Cercenedo E, Cervera C, Cisneros JM, Crespo-Leiro MG, Cuervas-Mons V, Elizalde-Jimenez, Fainas MC, Gavalda J, Goyanes MJ, Gutierrez-Gutierrez B, Hernandez D, Lien Q, Lopez-Andujar R, Lopez-Medrano F, Martin-Davila P, Montejo M, Moreno A, Oliver A, Pascual A, Perez-Nadaleas E, Roman-Brotto A, San-Juan R, Serson D, Sole-Jover A, Valerio M, Munoz P, Torre-Cisneros J, Spanish Society of T, Group for Study of Infection in Transplantation of the Spanish Society of Infectious D, Clinical M, Spanish Network for Research in Infectious D (2018) Management of multidrug resistant gram-negative bacilli infections in solid organ transplant recipients: SET/GEISTRA-SEIMC/REIPI recommendations. Transplant Rev (Orlando) 32:36–57

43. van Duin D, van Delden C, Practice ASTIDCo (2013) Multidrug-resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant 13(Suppl 4):31–41

44. Garrido RS, Aguado JM, Diaz-Pedroche C, Len O, Montejo M, Moreno A, Gurgui M, Torre-Cisneros J, Pareja F, Segovia J, Garcia M, Lumbresas C (2006) A review of critical periods for opportunistic infection in the new transplantation era. Transplantation 82:1457–1462

45. Helfrich M, Dorschner P, Thomas K, Stosor V, Ison MG (2017) A retrospective study to describe the epidemiology and outcomes of opportunistic infections after abdominal organ transplantation. Transplant Infect Dis. https://doi.org/10.1111/tid.12691

46. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, Humar A, The Transplantation Society International CMVC (2018) The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation 102:900–931

47. Florescu DF, Kalil AC, Qiu F, Grant W, Morris MC, Schmidt CM, Florescu MC, Poole JA (2014) Does increasing immunoglobulin levels impact survival in solid organ transplant recipients with hypogammaglobulinemia? Clin Transplant 28:1249–1255

48. Florescu DF, Kalil AC, Qiu F, Schmidt CM, Sandkoven Y (2013) What is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 13:2601–2610

49. Fishman JA (2014) From the classic concepts to modern practice. Clin Microbiol Infect 20(Suppl 7):1–9

50. Kupeli E, Eyyuboglu FO, Haberal M (2012) Pulmonary infections in transplant recipients. Curr Opin Pulm Med 18:202–212

51. De Gasperi A, Feltracco P, Ceravola E, Mazza E (2014) Pulmonary complications in patients receiving a solid-organ transplant. Curr Opin Crit Care 20:411–419

52. Lichtenstein DA, Mezieie GA (2008) Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest 134:117–125

53. Weiss E, Paugam-Burtz C, Jaber S (2018) Shock etiologies and fluid management in liver failure. Semin Respir Crit Care Med 39:538–545

54. Bailly S, Leroy Q, Montravers P, Constantin JM, Dupont H, Guillot L, Lortholary O, The Transplantation Society International CMVCG (2018) The impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 13:2601–2610
