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REVIEW

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.

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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. Pre-transplant 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].

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

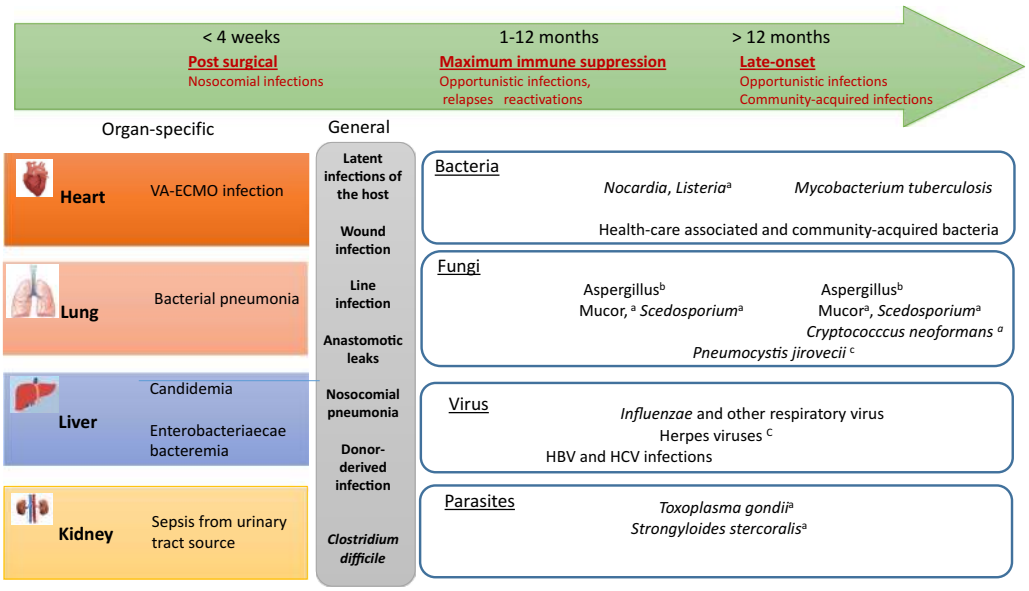

Fig. 1 Timeline of the main severe infections after solid-organ transplantation. **a** Low incidence in SOT recipients; **b** highest incidence in lung transplant recipients; **c** mostly in patients without effective prophylaxis

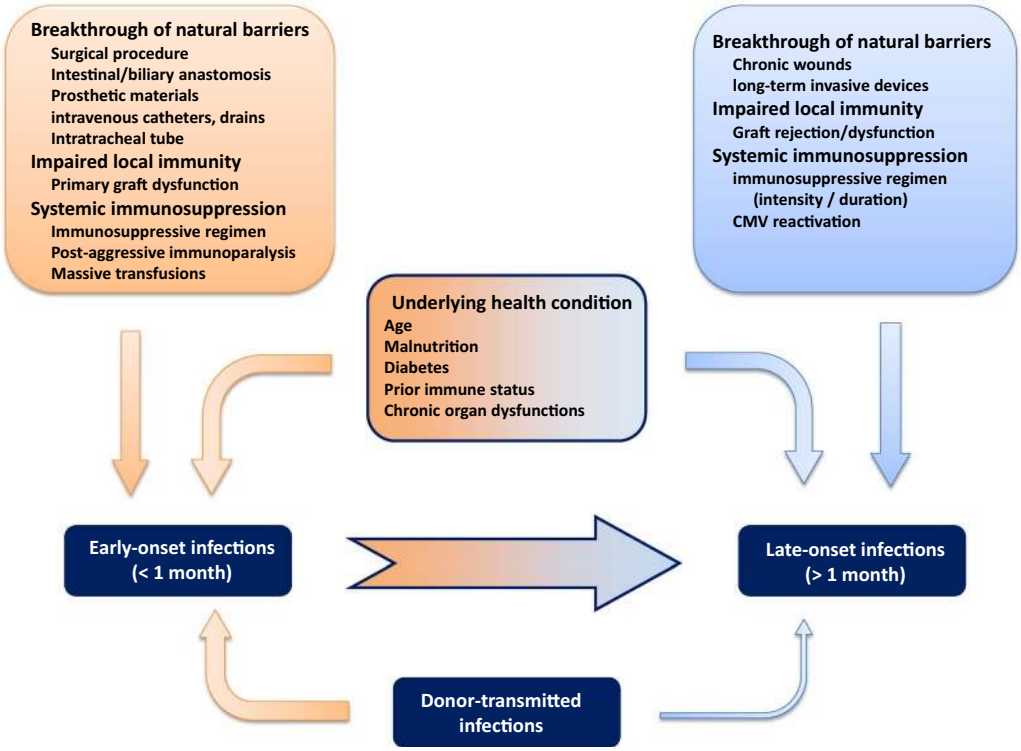

Fig. 2 Baseline and acquired determinants of infections in SOT recipients. The recipient's prior health condition accounts for the risk of infections throughout the post-transplantation period. Early-onset infections are related to acquired defense alterations including breakthrough of natural barriers and immune suppression. Late-onset infections are mostly related to the intensity of the immunosuppressive regimen

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 choledochojejunostomy 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

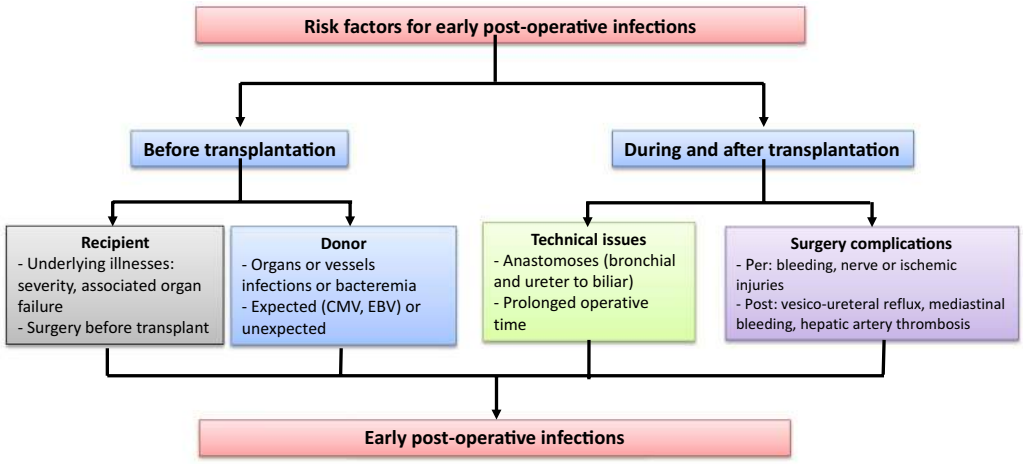

Fig. 3 Risk factors for early postoperative infections in SOT recipients. Risk factors that predispose to early postoperative infections in recipients of organ transplantation can be categorized as being present before transplant (recipient or donor) and those secondary to intraoperative or post-transplantation factors

developed to assess the IFN_γ 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 IFN_γ 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 IFN_γ 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].

Table 1 Prophylaxis in SOT patients

Pathogen	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 jirovecii*	All patients	TMP–SMX	3–6 months
	Candida spp.	Candiduria	Fluconazole	10–14 days
	Aspergillus spp.	Colonization, high-dose steroids, CMV infection, acute rejection	Aerosolized Amphotericin B, Voriconazole	4–6 weeks
Viruses	CMV	D+/R−, R+ receiving anti-thymocyte globulin at induction	Valganciclovir*	3–6 months
	HSV/VZV	D+ or R+	Valacyclovir**	3 months
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 jirovecii*	All patients	TMP-SMX	12 months
	Candida spp.	All patients	Fluconazole, echinocandin	14 days
	Aspergillus spp.	Colonization, high-dose steroids, 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
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 jirovecii*	All patients	TMP–SMX	6–12 months
	Candida spp.	All patients	Fluconazole, echinocandin	4 weeks
	Aspergillus spp.	Colonization, high-dose steroids, 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

Table 1 (continued)

Pathogen	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 jirovecii*	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 active azole*** (voriconazole, posaconazole or isavuconazole)	4–6 weeks
Virus	CMV	D+/R−, 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 jirovecii*	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+)

Table 1 (continued)

TMP-SMX trimethoprim-sulfamethoxazole, *D* donor, *R* recipient, *CMV* cytomegalovirus, *HSV* herpes simplex virus, *VZV* varicella zoster virus

*R+ without anti-thymocytes at induction can either be followed preemptively (CMV viremia every week) or receive valganciclovir prophylaxis for 3 months

**Only give valacyclovir if no valganciclovir is given for the prevention of CMV

***Choice dependent on liver toxicity

****Depending on local epidemiology

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

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
	Consolidation: bacterial infection or pulmonary hemorrhage
	Bronchopneumonia and peribronchiolar opacity: respiratory viruses, mycobacteria, *Mycoplasma*, *Chlamydia*, *Neisseria*, *Haemophilus* spp.
	Diffuse interstitial infiltrates: infection (*Pneumocystis jirovecii*, respiratory viruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus), graft rejection, lung edema, pulmonary hemorrhage, ARDS[a]
	Nodular infiltrates: bacteria, *Aspergillus* spp.
Lung ultrasound	Ultrasound patterns
	Consolidation: pneumonia, atelectasis
	Interstitial syndrome: infection, graft rejection, lung edema, pulmonary hemorrhage, ARDS[a]
Biomarkers	Rejection: circulating anti-HLA antibodies
	Infection: Procalcitonin, C-reactive protein
	Specific blood tests: galactomannan, β-D-glucan, specific PCR[b] for viruses, bacteria, parasites and fungi
Flexible bronchoscopy BAL[c]	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

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

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 pneumoniae *Neisseria meningitidis* Gram-negative bacilli *Listeria monocytogenes*	Acute onset Altered mental status ± neck stiffness ± fever	Pleocytosis (100–10,000/mm^3) Neutrophils High Pt; Low Glu	Normal or infarction Diffuse edema	Direct examination and culture (± 16 s RNA) mPCR	Blood cultures	Depending on clinical presentation
Mycobacterium tuberculosis	Subacute onset Altered mental status ± fever ± focal signs	Pleocytosis (100–1000/mm^3) Lymphocytes High Pt; Low Glu	Arachnoiditis Infarction Hydrocephalus Tuberculoma	Direct and culture (3–5 ml, repeat CSF analysis) PCR for *Mycobacterium tuberculosis* complex	QuantiFERON-TB	Pulmonary samples Brain biopsy
Nocardia spp.	Subacute onset ± fever Altered mental status ± focal signs ± extra neurologic involvement	Variable	Abscess(es)	CSF direct examination and culture (± 16s RNA)	Blood cultures	Skin biopsy (cultures) Respiratory samples Brain biopsy
Viruses						
Herpes simplex virus	Acute onset of altered mental status ± focal signs, ± fever, ± seizures	Pleocytosis (> 5/mm^3) 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/mm^3) Lymphocytes High Pt; Normal Glu	Ischemic lesions	PCR VZV	PCR VZV	Skin biopsy (PCR)
Cytomegalovirus	Subacute onset of altered mental status ± fever	Pleocytosis (> 5/mm^3) Lymphocytes High Pt; Normal Glu	Ventriculitis	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 Working-memory deficit	Pleocytosis (> 5/mm^3) 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 Abscess++	Direct examination and fungal cultures Galactomannan 1-3-β-D-glucan	Galactomannan 1-3-β-D-glucan	Pulmonary samples Skin biopsy Brain biopsy
Toxoplasma gondii	Altered mental status Focal signs ± fever ± seizure	Variable	Abscess(es)	PCR *Toxoplasma gondii*	PCR	Pulmonary samples + brain biopsy

Table 3 (continued)

Pathogen	Clinical picture	CSF findings	Brain imaging	CSF samples	Blood samples	Other samples
Cryptococcus neoformans	Sub-acute onset Altered mental status ± fever	Pleocytosis (100–1000/mm^3) Lymphocytes High Pt; low Glu	Normal Cryptococcoma	India ink stain and culture Cryptococcal antigen PCR	Blood cultures Cryptococcal antigen	Pulmonary samples

Pulmonary samples should be considered in patients with respiratory symptoms and/or lung involvement on imaging

Brain biopsy should be considered in patients presenting with focal lesion(s) with edema and mass effect in the absence of extra-CNS involvement and negative CSF analysis or contraindication to lumbar puncture because of risk of herniation

Skin biopsy should be considered in patients with skin lesion(s)

CSF cerebrospinal fluid, *PCR* polymerase chain reaction, *RNA* ribonucleic acid; *Glu* CSF glucose level, *Pt* CSF protein level

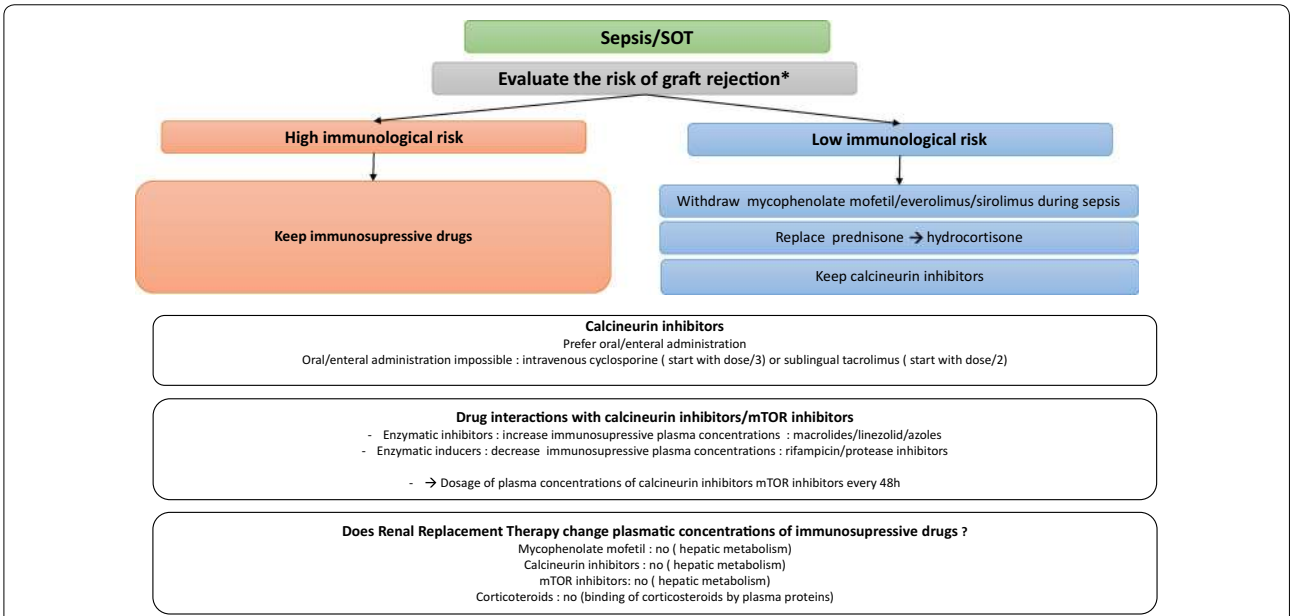

Fig. 4 Adaptation of the immunosuppressive drugs at the initial phase of sepsis: practical issues. *Immunologic risk assessment: deceased donor, number of human leukocyte antigen (HLA) mismatches, donor-specific antibodies (DSA), organ-specific differences (heart-lung > kidney > liver). Withdrawal of IS drugs should be discussed in close collaboration with transplant physicians

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*

pneumoniae (CRKP) as well as gram-positive organisms, such as vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).

Colonization with MDR organisms, acquired prior to transplantation, may include bacteria that could be resistant to agents used regularly for surgical prophylaxis. On this basis, some important points for management of SOT recipients should be routinely assessed: (1) resistance profiles of all isolates (colonizers and pathogens) should be obtained; (2) donor colonization should not constitute a contraindication to transplantation; however, donation should be avoided from donors with CRE bacteremic infections as well as kidney grafts from donors with CRE urinary tract infections and lung grafts from donors with CRE lung infections; (3) recipient colonization is associated with an increased risk of infection, but it is not considered a contraindication to SOT; (4) different surgical prophylaxis regimens are not recommended for patients colonized with carbapenem-resistant pathogens; (5) detection of carriers, contact isolation precautions, hand hygiene compliance and antibiotic control policies are important measures to prevent MDR infections [42].

Some other important considerations should be reported: colonized lung transplant recipients could benefit from prophylactic inhaled antibiotics, especially for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* infection; colonized SOT recipients should receive an empirical treatment that includes active antibiotics, and directed therapy should be adjusted according to susceptibility and disease severity. Finally, no data are currently available about potential benefit of intestinal decolonization [85].

Therapeutic rules are similar in SOT recipients and other ICU patients [86]. Three points should therefore be pointed out: (1) SOT recipients have a higher risk of infections due to MDR bacterias [87]. (2) Pharmacologic interactions and multiple drug exposures may expose patients to an increased risk of inadequate dosing and toxicities. (3) The shortening of treatment duration is not demonstrated in SOT recipients and should be discussed on an individual basis [88, 89].

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 candidiasis 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-D-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

Table 4 Diagnostic strategy in SOT recipients with suspected invasive fungal disease (IFD) based on clinical presentation

	Fever with no respiratory signs or symptoms	Nodular[a] 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
Most typical clinical setting, including main risk factors	Early after SOT Liver, small bowel, pancreas transplant Reoperation and re-transplantation Antibiotic administration Dialysis	Lung[b] 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 Uncontrolled diabetes Renal failure Iron overload in liver transplant
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 AND surgical debridement
Length of treatment	For candidemia 14 days after the first negative blood culture	At least 12 weeks	3 weeks, secondary prophylaxis usually warranted	Individualized, at least 12 weeks

BDG beta-D-glucan, *GM* galactomannan, *L-AmB* liposomal amphotericin B, *NPV* negative predictive value, *PjP* Pneumocystis jirovecii pneumonia, *SMX*, sulfamethoxazole, *TMP* trimethoprim

[a] 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)

[b] 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 after transplantation in patients without prevention, but may be delayed in patients with prophylaxis. CMV disease (defined as evidence of CMV infection with attributable symptoms [46]) may present as isolated fever, cytopenia or organ involvement (colitis or enteritis, pneumonia, hepatitis or less frequently myocarditis, pancreatitis or central nervous system involvement) and is usually preceded by virus reactivation [5]. Moreover, CMV disease is associated with an increased rate of bacterial and fungal infections (due to virus-induced immunosuppression [3, 4]) and post-transplant lymphoproliferative disorders [105]. Curative treatment of CMV disease or CMV organ involvement includes the use of intravenous ganciclovir, duration depending on the clinical picture and kinetics of viral load, but for at least 2–3 weeks, and reduction of immunosuppression [46]. The rate of CMV disease has decreased with preventive measures (prophylaxis and preemptive treatment). Prophylaxis, routinely recommended for all transplants from CMV IgG-positive donors (D+) to CMV IgG-negative recipients (R−), consists of valganciclovir or ganciclovir administration during a given period (generally 3–12 months, depending on the organ grafted) [46]. Preemptive treatment is based on viral load surveillance (CMV-DNA testing) and treatment when the virus load exceeds a specific threshold. However, thresholds for triggering antiviral therapy are not standardized, but range between 1500 and 4000 IU/ml [1]. This should be adapted according to organ and individual risk. CMV IgG-negative recipients (R−) of organs from negative donors (D−) should not receive prophylaxis or be monitored for CMV reactivation, but tested in case of clinical suspicion [46]. The best strategies (prophylaxis or preemptive treatment) depending on donor/recipient serostatus and transplant types are summarized in Table 1 [46]. Other herpesviridae (HSV, EBV) are less frequent or lead to less severe disease.

SOT is, like other immunosuppressive conditions, a risk factor for severe influenza disease [106]. A recent multicenter study showed that influenza pneumonia was frequent in SOT recipients [107], but its incidence might be decreased, as well as the need for ICU admission, by influenza vaccination and early antiviral therapy [107]. An influenza vaccination strategy should be adapted in SOT recipients: compared with single simple dose, high dose [108] or double dose regimens (given 5 weeks apart) [109] were associated with increased antibody response. Non-influenza respiratory viruses (rhinoviruses, coronaviruses, human metapneumovirus, respiratory syncytial virus and adenoviruses) may also be responsible for severe respiratory infection, especially in lung transplant 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 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. kansasii*, *M. haemophilum* and *M. marinum* and the rapid-growing *M. fortuitum*, *M. chelonae* 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 ≥ 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 entities 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*, *Coccidioides* spp., *Paracoccidioides* spp., *Blastomyces dermatitidis*, *Cryptococcus gattii*) can 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*, *Encephalitozoon cuniculi* (causing microsporidiosis), *Strongyloides stercoralis*, *Echinococcus granulosus*, *Filariae* 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

Conflicts of interest

MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Biomerieux, Cidara, Gilead, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine

Company, Shionogi, Tetraphase, VenatoRx and Vifor. RF reports participation in scientific advisory boards: MSD, Shionogi and lectures: Beckton-Dickinson, MSD, Astelas, Pfizer, Thermo, Estor. SJ reports receiving consulting fees from Drager, Hamilton, Maquet, Medtronic and Fisher & Paykel. CEL reports participations in advisory boards (Bayer Healthcare, Carmat, Faron, ThermoFischer Brahms) and lectures (MSD, Nihon-Koden, Biomérieux). 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 lecture fees paid to his institution by ALEXION. JFT reports participation to scientific advisory boards (Astra-Zeneca, Pfizer, MSD, Nabriva, Gilead), lectures (Biomerieux, MSD, Astelas, 3M, 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 AY, Levvey BJ, Meiser B, Rossano JW, Chambers DC, Yusen RD, Stehlik 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. Kalil 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. Kalil AC, Dakroub 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 17:856–879
6. Poole D, Skurzak 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, Radjou A, Lebut J, Dilly MP, Mourvillier B, Dorent R, Nataf P, Wolff M, Timsit JF (2019) Infectious complications following heart transplantation in the era of high-priority allocation and extracorporeal membrane oxygenation. Ann Intensive Care 9:17
8. Hsu J, Griffith BP, Dowling RD, Kormos RL, Dummer JS, Armitage JM, Zenati M, Hardesty RL (1989) Infections in mortally ill cardiac transplant recipients. J Thorac Cardiovasc Surg 98:506–509
9. Valapour M, Lehr CJ, Skeans MA, Smith JM, Carrico R, Uccellini K, Lehman R, Robinson A, Israni AK, Snyder JJ, Kasiske BL (2018) OPTN/SRTR 2016 annual data report: lung. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 18(Suppl 1):363–433
10. Zalawadiya S, Fudim M, Bhat G, Cotts W, Lindenfeld J (2017) Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. J Heart Lung Transplant Off Publ Int Soc Heart Transplant 36:77–81
11. Dorschner P, McElroy LM, Ison MG (2014) Nosocomial infections within the first month of solid organ transplantation. Transpl Infect Dis Off J Transplant Soc 16:171–187
12. Green M (2013) Introduction: infections in solid organ transplantation. Am J Transplant 13(Suppl 4):3–8
13. Chuang P, Parikh CR, Langone A (2005) Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. Clin Transplant 19:230–235
14. Koivusalo A, Isoniemi H, Salmela K, Hockerstedt K (1994) Biliary complications in 100 adult liver transplantations: a retrospective clinical study. Transpl Int 7(Suppl 1):S119–S120
15. Kusne S, Dummer JS, Singh N, Iwatsuki S, Makowka L, Esquivel C, Tzakis AG, Starzl TE, Ho M (1988) Infections after liver transplantation. An analysis of 101 consecutive cases. Medicine (Baltimore) 67:132–143
16. Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, Gordon F, O'Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arterburn S, Svarovskaia E, Moonka D, Afdhal N (2015) Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 148(100–107):e101
17. Levitsky J, Verna EC, O'Leary JG, Bzowej NH, Moonka DK, Hyland RH, Arterburn S, Dvory-Sobol H, Brainard DM, McHutchison JG, Terrault NA (2016) Perioperative ledipasvir–sofosbuvir for HCV in liver-transplant recipients. N Engl J Med 375:2106–2108
18. Myers TJ, Khan T, Frazier OH (2000) Infectious complications associated with ventricular assist systems. ASAIO J 46:S28–S36
19. De Vlaminck I, Martin L, Kertesz M, Patel K, Kowarsky M, Strehl C, Cohen G, Luikart H, Neff NF, Okamoto J, Nicolls MR, Cornfield D, Weill D, Valantine H, Khush KK, Quake SR (2015) Noninvasive monitoring of infection and rejection after lung transplantation. Proc Natl Acad Sci USA 112:13336–13341
20. Goldberg DS, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, Bloom RD, Nazarian SM, Sawinski D, Porrett P, Naji A, Hasz R, Suplee L, Trofe-Clark J, Sicilia A, McCauley M, Farooqi M, Gentile C, Smith J, Reese PP (2017) Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med 376:2394–2395
21. Ison MG, Hager J, Blumberg E, Burdick J, Carney K, Cutler J, Dimaio JM, Hasz R, Kuehnert MJ, Ortiz-Rios E, 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
22. Mularoni A, Bertani A, Vizzini G, Gona F, Campanella M, Spada M, Gruttadauria 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
23. Levesque E, Suet G, Merle JC, Compagnon P, Amathieu R, Feray C, Botterel F, Foulet F, Azoulay D, Dhonneur G (2014) Candida vascular complication in a liver transplant recipient due to yeast contamination of preservation solution. Transpl Infect Dis Off J Transplant Soc 16:827–829
24. Mittal C, Hassan S, Arshad S, Jeepalyam S, Bruni S, Miceli 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
25. Hsu RB, Chang CI, 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
26. Wan Q, Ye Q, Zhou J (2013) Mortality predictors of bloodstream infections in solid-organ transplant recipients. Exp Clin Transplant 11:211–214
27. Florescu DF, Sandkovsky U, Kalil AC (2017) Sepsis and challenging infections in the immunosuppressed patient in the intensive care unit. Infect Dis Clin N Am 31:415–434
28. Trzeciak S, Sharer R, Piper 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
29. Kalil 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
30. Bodro M, Sabe N, Tubau F, Llado L, Baliellas C, Roca J, Cruzado JM, Carratala J (2013) Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. Transplantation 96:843–849
31. Canet E, Zafrani L, Azoulay E (2016) The critically ill kidney transplant recipient: a narrative review. Chest 149:1546–1555
32. Azoulay E, Pickkers P, Soares M, Perner A, Rello J, Bauer PR, van de Louw A, Hemelaar P, Lemiale V, Taccone FS, Martin Loeches I, Meyhoff TS, Salluh J, Schellongowski P, Rusinova K, Terzi N, Mehta S, Antonelli M, Kouatchet A, Barratt-Due A, Valkonen M, Landburg PP, Bruneel F, Bukan RB, Pene F, Metaxa V, Moreau AS, Souppart V, Burghi G, Girault C, Silva

UVA, Montini L, Barbier F, Nielsen LB, Gaborit B, Mokart D, Chevret S (2017) Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. Intensive Care Med 43:1808–1819
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
34. Zeyneloglu P (2015) Respiratory complications after solid-organ transplantation. Exp Clin Transplant 13:115–125
35. Fernandez-Ruiz M, Lopez-Medrano F, Romo EM, Allende LM, Meneu JC, Fundora-Suarez Y, San-Juan R, Lizasoain M, Paz-Artal E, Aguado JM (2009) Pretransplant lymphocyte count predicts the incidence of infection during 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, Snydman DR (2014) Pretransplant lymphopenia is a novel prognostic factor in cytomegalovirus and noncytomegalovirus invasive infections after liver transplantation. Liver Transpl 20:1497–1507
37. Sarmiento E, Navarro J, Fernandez-Yanez J, Palomo J, Munoz P, Carbone J (2014) Evaluation of an immunological score to assess the risk of severe infection in heart recipients. Transpl Infect Dis 16:802–812
38. Calarota SA, Zelini P, De Silvestri A, Chiesa A, Comolli G, Sarchi E, Migotto C, Pellegrini C, Esposito P, Minoli L, Tinelli C, Marone P, Baldanti F (2012) Kinetics of T-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, Lumbreras 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 27:674–685
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, Humar A, Kumar D (2018) Evaluation of a novel global immunity assay to predict infection in organ transplant recipients. Clin Infect Dis 66:1392–1397
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, Cercenado E, Cervera C, Cisneros JM, Crespo-Leiro MG, Cuervas-Mons V, Elizalde-Fernandez J, Farinas MC, Gavalda J, Goyanes MJ, Gutierrez-Gutierrez B, Hernandez D, Len O, Lopez-Andujar R, Lopez-Medrano F, Martin-Davila P, Montejo M, Moreno A, Oliver A, Pascual A, Perez-Nadales E, Roman-Broto A, San-Juan R, Seron 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/GESITRA-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, Lumbreras 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. Transpl 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 CMVCG (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, Sandkovsky U (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):4–9
50. Kupeli E, Eyuboglu 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, Meziere 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 O, Montravers P, Constantin JM, Dupont H, Guillemot D, Lortholary O, Mira JP, Perrigault PF, Gangneux JP, Azoulay E, Timsit JF (2015) Antifungal de-escalation was not associated with adverse outcome in critically ill patients treated for invasive candidiasis: post hoc analyses of the AmarCAND2 study data. Intensive Care Med 41:1931–1940
55. Benoit DD, Doig G, Timsit JF (2016) Focus on adequate antimicrobial treatment and de-escalation in the ICU. Intensive Care Med 42:1856–1858
56. Jung B, Cisse M, Chanques G, Arsac E, Bismuth M, Panaro F, Perrigault PF, Souche B, Gallix B, Verzilli D, Delay JM, Navarro F, Pageaux GP, Jaber S (2011) Causes of early mortality after liver transplantation: a twenty-years single centre experience. Ann Fr Anesth Reanim 30:899–904
57. Kalil AC, Opal SM (2015) Sepsis in the severely immunocompromised patient. Curr Infect Dis Rep 17:487
58. Schachtner T, Stein M, Reinke P (2017) Sepsis after renal transplantation: clinical, immunological, and microbiological risk factors. Transpl Infect Dis Off J Transplant Soc. https://doi.org/10.1111/tid.12695
59. Trofe-Clark J, Lemonovich TL (2013) Interactions between anti-infective agents and immunosuppressants in solid organ transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 13(Suppl 4):318–326
60. Hamandi B, Holbrook AM, Humar A, Brunton J, Papadimitropoulos EA, Wong GG, Thabane L (2009) Delay of adequate empiric antibiotic therapy is associated with increased mortality among solid-organ transplant patients. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 9:1657–1665
61. de Carvalho MA, Freitas FG, Silva Junior HT, Bafi AT, Machado FR, Pestana JO (2014) Mortality predictors in renal transplant recipients with severe sepsis and septic shock. PLoS ONE 9:e111610
62. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL (2016) Sepsis and septic shock. Nat Rev Dis Prim 2:16045
63. Tu GW, Ju MJ, Zheng YJ, Zhu DM, Xu M, Rong RM, Zhu TY, Luo Z (2014) An interdisciplinary approach for renal transplant recipients with severe pneumonia: a single ICU experience. Intensive care Med 40:914–915
64. Bige N, Zafrani L, Lambert J, Peraldi MN, Snanoudj R, Reuter D, Legendre C, Chevret S, Lemiale V, Schlemmer B, Azoulay E, Canet E (2014) Severe infections requiring intensive care unit admission in kidney transplant recipients: impact on graft outcome. Transpl Infect Dis Off J Transplant Soc 16:588–596
65. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, Francois B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohe J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E (2018) Hydrocortisone plus fludrocortisone for adults with septic shock. New Engl J Med 378:809–818
66. Patel MS, Niemann CU, Sally MB, De La Cruz S, Zatarain J, Ewing T, Crutchfield M, Enestvedt CK, Malinoski DJ (2015) The impact of hydroxyethyl starch use in deceased organ donors on the development of delayed graft function in kidney transplant recipients: a propensity-adjusted analysis. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 15:2152–2158

67. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377
68. Bafi AT, Tomotani DY, de Freitas FG (2017) Sepsis in solid-organ transplant patients. Shock 47:12–16
69. Wright AJ, Fishman JA (2014) Central nervous system syndromes in solid organ transplant recipients. Clin Infect Dis Off Publ Infect Dis Soc Am 59:1001–1011
70. Sonneville R, Magalhaes E, Meyfroidt G (2017) Central nervous system infections in immunocompromised patients. Curr Opin Crit Care 23:128–133
71. Sonneville R, Mariotte E, Brouwer MC (2019) Cerebral complications of solid organ transplantation. Intensive Care Med. https://doi.org/10.1007/s00134-019-05540-1
72. McCarthy M, Rosengart A, Schuetz AN, Kontoyiannis DP, Walsh TJ (2014) Mold infections of the central nervous system. New Engl J Med 371:150–160
73. Brouwer MC, Tunkel AR, van de Beek D (2014) Brain abscess. New Engl J Med 371:1758
74. Marzolf G, Sabou M, Lannes B, Cotton F, Meyronet D, Galanaud D, Cottier JP, Grand S, Desal H, Kreutz J, Schenck M, Meyer N, Schneider F, Dietemann JL, Koob M, Herbrecht R, Kremer S (2016) Magnetic resonance imaging of cerebral aspergillosis: imaging and pathological correlations. PLoS ONE 11:e0152475
75. Coussement J, Lebeaux D, van Delden C, Guillot H, Freund R, Marbus S, Melica G, Van Wijngaerden E, Douvry B, Van Laecke S, Vuotto F, Tricot L, Fernandez-Ruiz M, Dantal J, Hirzel C, Jais JP, Rodriguez-Nava V, Lortholary O, Jacobs F (2016) Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. Clin Infect Dis Off Publ Infect Dis Soc Am 63:338–345
76. Coussement J, Lebeaux D, Rouzaud C, Lortholary O (2017) Nocardia infections in solid organ and hematopoietic stem cell transplant recipients. Current Opin Infect Dis 30:545–551
77. Schmidt M, Sonneville R, Schnell D, Bige N, Hamidfar R, Mongardon N, Castelain V, Razazi K, Marty A, Vincent F, Dres M, Gaudry S, Luyt CE, Das V, Micol JB, Demoule A, Mayaux J (2013) Clinical features and outcomes in patients with disseminated toxoplasmosis admitted to intensive care: a multicenter study. Clinl Infect Dis Off Publ Infect Dis Soc Am 57:1535–1541
78. Fernandez-Sabe N, Cervera C, Farinas MC, Bodro M, Munoz P, Gurgui M, Torre-Cisneros J, Martin-Davila P, Noblejas A, Len O, Garcia-Reyne A, Del Pozo JL, Carratala J (2012) Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. Clin Infect Dis Off Publ Infect Dis Soc Am 54:355–361
79. van Veen KE, Brouwer MC, van der Ende A, van de Beek D (2016) Bacterial meningitis in solid organ transplant recipients: a population-based prospective study. Transpl Infect Dis Off J Transplant Soc 18:674–680
80. George IA, Santos CAQ, Olsen MA, Powderly WG (2017) Epidemiology of cryptococcosis and cryptococcal meningitis in a large retrospective cohort of patients after solid organ transplantation. Open Forum Infect Dis 4:ofx004
81. Cantier M, Morisot A, Guerot E, Megarbane B, Razazi K, Contou D, Mariotte E, Canet E, De Montmollin E, Dubee V, Boulet E, Gaudry S, Voiriot G, Mayaux J, Pene F, Neuville M, Mourvillier B, Ruckly S, Bouadma L, Wolff M, Timsit JF, Sonneville R (2018) Functional outcomes in adults with tuberculous meningitis admitted to the ICU: a multicenter cohort study. Crit Care 22:210
82. Saylor D, Thakur K, Venkatesan A (2015) Acute encephalitis in the immunocompromised individual. Curr Opin Infect Dis 28:330–336
83. Mateen FJ, Muralidharan R, Carone M, van de Beek D, Harrison DM, Aksamit AJ, Gould MS, Clifford DB, Nath A (2011) Progressive multifocal leukoencephalopathy in transplant recipients. Ann Neurol 70:305–322
84. Silva JT, Fernandez-Ruiz M, Aguado JM (2018) Multidrug-resistant gram-negative infection in solid organ transplant recipients: implications for outcome and treatment. Curr Opin Infect Dis 31:499–505
85. Qiao B, Wu J, Wan Q, Zhang S, Ye Q (2017) Factors influencing mortality in abdominal solid organ transplant recipients with multidrug-resistant gram-negative bacteremia. BMC Infect Dis 17:171
86. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, Kipnis E, Kollef M, Laupland K, Paiva JA, Rodriguez-Bano J, Ruppe E, Salluh J, Taccone FS, Weiss E, Barbier F (2019) Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive Care Med 45:172–189
87. Camargo LF, Marra AR, Pignatari AC, Sukiennik T, Behar PP, Medeiros EA, Ribeiro J, Girao E, Correa L, Guerra C, Brites C, Pereira CA, Carneiro I, Reis M, Souza MA, Barata CU, Edmond MB (2015) Nosocomial bloodstream infections in a nationwide study: comparison between solid organ transplant patients and the general population. Transpl Infect Dis Off J Transplant Soc 17:308–313
88. Kritikos A, Manuel O (2016) Bloodstream infections after solid-organ transplantation. Virulence 7:329–340
89. Cervera C, van Delden C, Gavalda J, Welte T, Akova M, Carratala J (2014) Multidrug-resistant bacteria in solid organ transplant recipients. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Diss 20(Suppl 7):49–73
90. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, Pfaller M, Steinbach WJ, Webster KM, Marr KA (2010) Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis Off J Transplant Soc 12:220–229
91. Husain S, Silveira FP, Azie N, Franks B, Horn D (2017) Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance (R) registry analysis. Med Mycol 55:269–277
92. Albano L, Bretagne S, Mamzer-Bruneel MF, Kacso I, Desnos-Ollivier M, Guerrini P, Le Luong T, Cassuto E, Dromer F, Lortholary O (2009) Evidence that graft-site candidiasis after kidney transplantation is acquired during organ recovery: a multicenter study in France. Clin Infect Dis Off Publ Infect Dis Soc Am 48:194–202
93. Camargo JF (2017) Donor-derived infections in solid organ transplant recipients: challenging the 30-day paradigm. Transpl Infect Disease Off J Transplant Soc. https://doi.org/10.1111/tid.12665
94. Kusne S, Taranto S, Covington S, Kaul DR, Blumberg EA, Wolfe C, Green M (2016) Coccidioidomycosis transmission through organ transplantation: a report of the OPTN ad hoc disease transmission advisory committee. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg 16:3562–3567
95. Singh N, Perfect JR (2007) Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis 7:395–401
96. Sun HY, Alexander BD, Huprikar S, Forrest GN, Bruno D, Lyon GM, Wray D, Johnson LB, Sifri CD, Razonable RR, Morris MI, Stosor V, Wagener MM, Singh N (2015) Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: implications for the management of immunosuppression. Clin Infect Dis Off Publ Infect Dis Soc Am 60:36–44
97. Scemla A, Gerber S, Duquesne A, Parize P, Martinez F, Anglicheau D, Snanoudj R, Zuber M, Bougnoux ME, Legendre C, Lortholary O (2015) Dramatic improvement of severe cryptococcosis-induced immune reconstitution syndrome with adalimumab in a renal transplant recipient. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 15:560–564
98. Andes DR, Safdar N, Baddley JW, Alexander B, Brumble L, Freifeld A, Hadley S, Herwaldt L, Kauffman C, Lyon GM, Morrison V, Patterson T, Perl T, Walker R, Hess T, Chiller T, Pappas PG (2016) The epidemiology and outcomes of invasive Candida infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Transpl Infect Dis Off J Transplant Soc 18:921–931
99. Mutschlechner W, Risslegger B, Willinger B, Hoenigl M, Bucher B, Eschertzhuber S, Lass-Florl C (2015) Bronchoalveolar lavage fluid (1,3) beta-d-glucan for the diagnosis of invasive fungal infections in solid organ transplantation: a prospective multicenter study. Transplantation 99:e140–e144

100. Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, Carver PL, van Delden C, Merino E, Perez-Saez MJ, Montero M, Coussement J, de Abreu Mazzolin M, Cervera C, Santos L, Sabe N, Scemla A, Cordero E, Cruzado-Vega L, Martin-Moreno PL, Len O, Rudas E, de Leon AP, Arriola M, Lauzurica R, David M, Gonzalez-Rico C, Henriquez-Palop F, Fortun J, Nucci M, Manuel O, Pano-Pardo JR, Montejo M, Munoz P, Sanchez-Sobrino B, Mazuecos A, Pascual J, Horcajada JP, Lecompte T, Moreno A, Carratala J, Blanes M, Hernandez D, Farinas MC, Andres A, Aguado JM (2016) Clinical presentation and determinants of mortality of invasive pulmonary aspergillosis in kidney transplant recipients: a multinational cohort study. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 16:3220–3234
101. Barchiesi F, Mazzocato S, Mazzanti S, Gesuita R, Skrami E, Fiorentini A, Singh N (2015) Invasive aspergillosis in liver transplant recipients: epidemiology, clinical characteristics, treatment, and outcomes in 116 cases. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 21:204–212
102. Iriart X, Challan Belval T, Fillaux J, Esposito L, Lavergne RA, Cardeau-Desangles I, Roques O, Del Bello A, Cointault O, Lavayssiere L, Chauvin P, Menard S, Magnaval JF, Cassaing S, Rostaing L, Kamar N, Berry A (2015) Risk factors of pneumocystis pneumonia in solid organ recipients in the era of the common use of posttransplantation prophylaxis. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 15:190–199
103. Werbel WA, Ison MG, Angarone MP, Yang A, Stosor V (2018) Lymphopenia is associated with late onset *Pneumocystis jirovecii* pneumonia in solid organ transplantation. Transpl Infect Dis Off J Transplant Soc 20:e12876
104. Neofytos D, Hirzel C, Boely E, Lecompte T, Khanna N, Mueller NJ, Boggian K, Cusini A, Manuel O, van Delden C (2018) *Pneumocystis jirovecii* pneumonia in solid organ transplant recipients: a descriptive analysis for the Swiss Transplant Cohort. Transpl Infect Dis Off J Transplant Soc 20:e12984
105. Hodson EM, Jones CA, Webster AC, Strippoli GF, Barclay PG, Kable K, Vimalachandra D, Craig JC (2005) Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials. Lancet 365:2105–2115
106. Martin-Loeches I, Schultz MJ, Vincent JL, Alvarez-Lerma F, Bos LD, Sole-Violan J, Torres A, Rodriguez A (2017) Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med 43:48–58
107. Kumar D, Ferreira VH, Blumberg E, Silveira F, Cordero E, Perez-Romero P, Aydillo T, Danziger-Isakov L, Limaye AP, Carratala J, Munoz P, Montejo M, Lopez-Medrano F, Farinas MC, Gavalda J, Moreno A, Levi M, Fortun J, Torre-Cisneros J, Englund JA, Natori Y, Husain S, Reid G, Sharma TS, Humar A (2018) A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. Clin Infect Dis Off Publ Infect Dis Soc Am 67:1322–1329
108. Natori Y, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, Rotstein C, Lilly L, Schiff J, Singer L, Humar A, Kumar D (2018) A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult solid-organ transplant recipients. Clin Infect Dis Off Publ Infect Dis Soc Am 66:1698–1704
109. Cordero E, Roca-Oporto C, Bulnes-Ramos A, Aydillo T, Gavalda J, Moreno A, Torre-Cisneros J, Montejo JM, Fortun J, Munoz P, Sabe N, Farinas MC, Blanes-Julia M, Lopez-Medrano F, Suarez-Benjumea A, Martinez-Atienza J, Rosso-Fernandez C, Perez-Romero P (2017) Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1-2, a randomized controlled clinical trial. Clin Infect Dis Off Publ Infect Dis Soc Am 64:829–838
110. Paulsen GC, Danziger-Isakov L (2017) Respiratory viral infections in solid organ and hematopoietic stem cell transplantation. Clin Chest Med 38:707–726
111. Grim SA, Reid GE, Clark NM (2017) Update in the treatment of non-influenza respiratory virus infection in solid organ transplant recipients. Expt Opin Pharmacother 18:767–779
112. Peghin M, Los-Arcos I, Hirsch HH, Codina G, Monforte V, Bravo C, Berastegui C, Jauregui A, Romero L, Cabral E, Ferrer R, Sacanell J, Roman A, Len O, Gavalda J (2018) Community-acquired respiratory viruses are a risk factor for chronic lung allograft dysfunction. Clin Infect Dis Off Publ Infect Dis Soc Am
113. Kalil AC, Sandkovsky U, Florescu DF (2018) Severe infections in critically ill solid organ transplant recipients. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 24:1257–1263
114. Keating MR, Daly JS (2013) Nontuberculous mycobacterial infections in solid organ transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 13(Suppl 4):77–82
115. Osmani M, Sotello D, Alvarez S, Odell JA, Thomas M (2018) Mycobacterium abscessus infections in lung transplant recipients: 15-year experience from a single institution. Transpl Infect Dis Off J Transplant Soc 20(2):e12835
116. Huang HC, Weigt SS, Derhovanessian A, Palchevskiy V, Ardehali A, Saggar R, Kubak B, Gregson A, Ross DJ, Lynch JP 3rd, Elashoff R, Belperio JA (2011) Non-tuberculous mycobacterium infection after lung transplantation is associated with increased mortality. J Heart Lung Transplant Off Publ Int Soc Heart Transplant 30:790–798
117. Saliba F, Delvart V, Ichai P, Kassis N, Botterel F, Mihaila L, Azoulay D, Adam R, Castaing D, Bretagne S, Samuel D (2013) Fungal infections after liver transplantation: outcomes and risk factors revisited in the MELD era. Clin Transplant 27:E454–E461
118. Len O, Garzoni C, Lumbreras C, Molina I, Meije Y, Pahissa A, Grossi P (2014) Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor-derived infections. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 20(Suppl 7):10–18
119. Fishman JA, Greenwald MA, Grossi PA (2012) Transmission of infection with human allografts: essential considerations in donor screening. Clin Infect Dis Off Publ Infect Dis Soc Am 55:720–727