


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

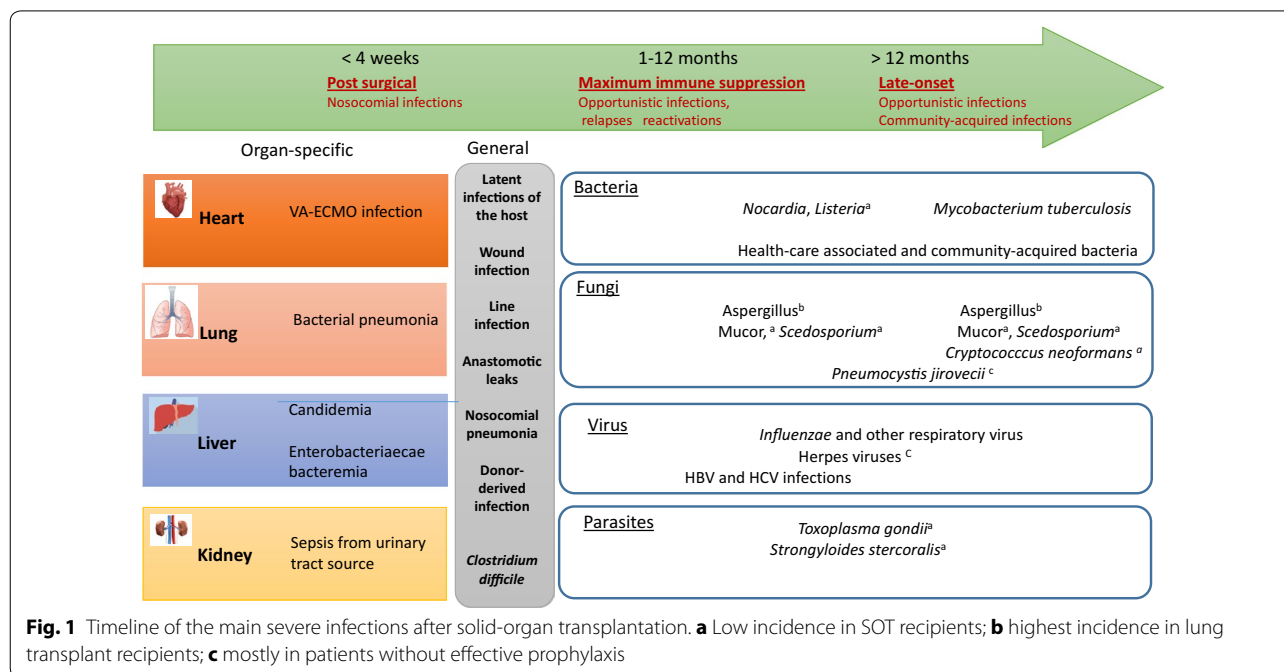
Infections represent the main cause of death within 1 year after heart or lung transplantation, accounting for 32% and 35% of deaths during this period, respectively. Although with a lesser incidence, infections remain an important cause of death and/or loss of graft survival [1]. The susceptibility 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

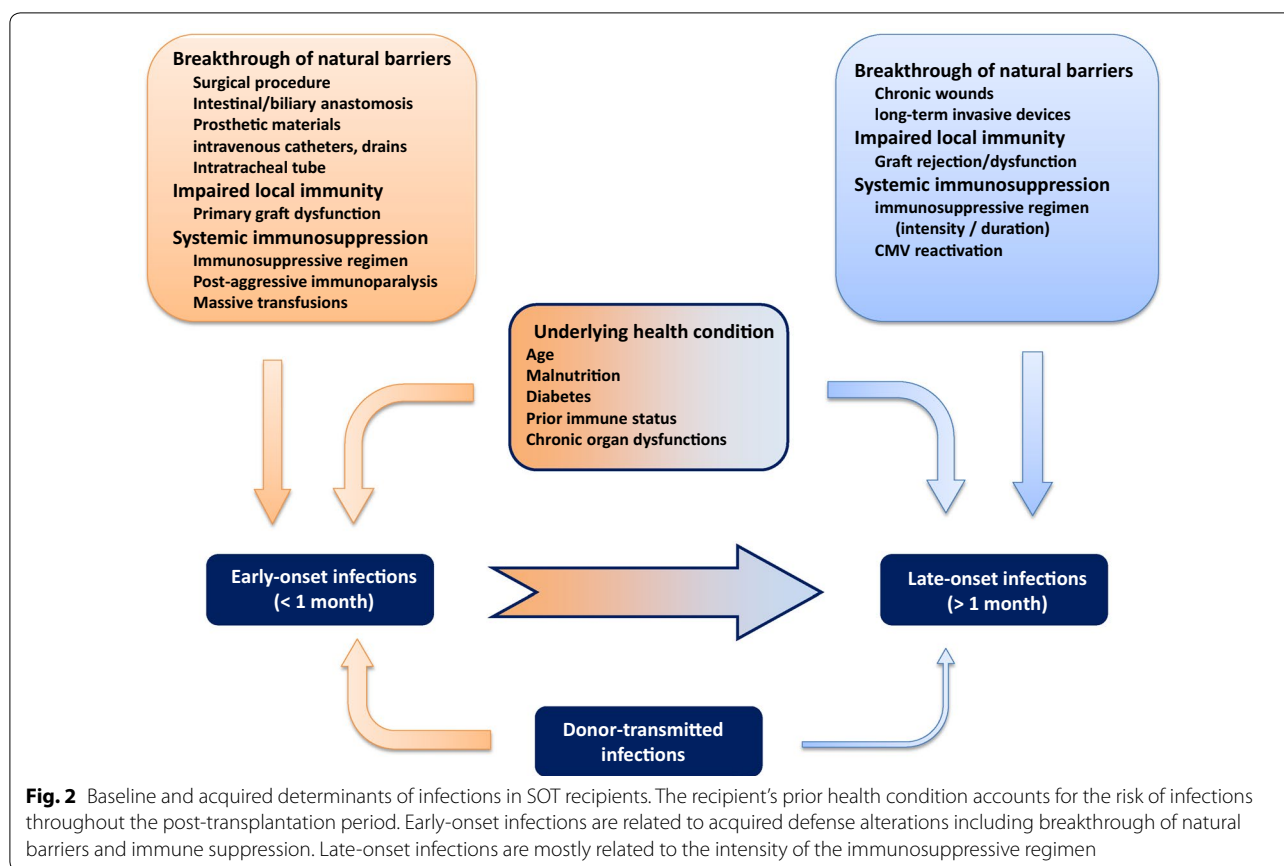
Take-home messages

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

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].





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 multi-drug-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

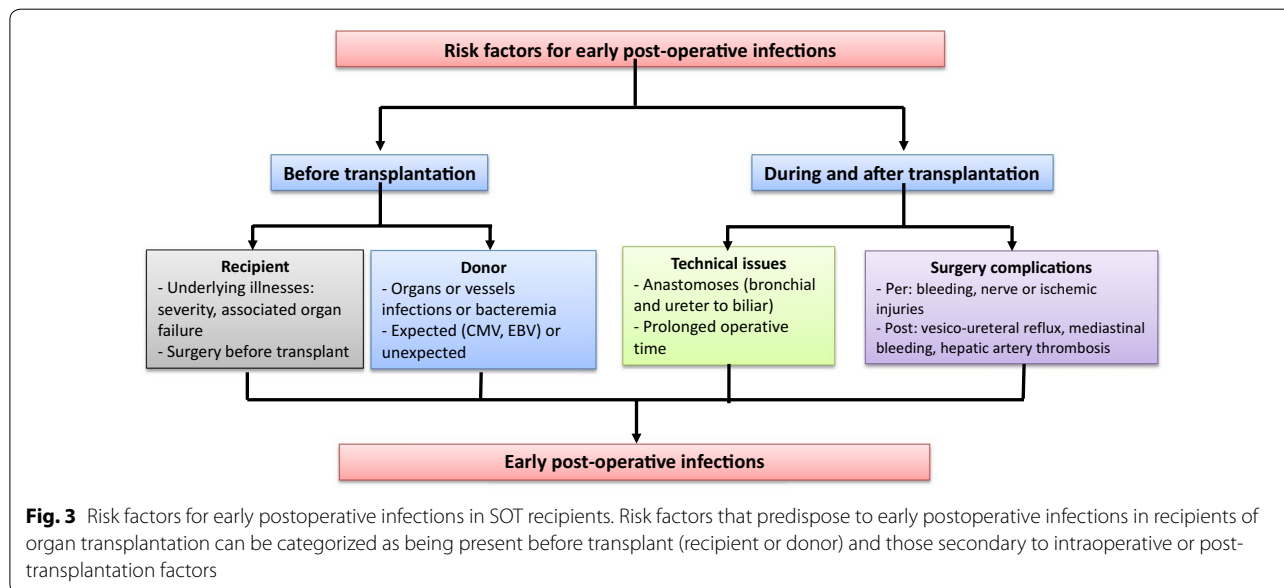


Fig. 3 Risk factors for early postoperative infections in SOT recipients. Risk factors that predispose to early postoperative infections in recipients of organ transplantation can be categorized as being present before transplant (recipient or donor) and those secondary to intraoperative or post-transplantation 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
<i>Kidney recipients</i>				
Bacteria	<i>Enterobacteriaceae</i>	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	<i>Pneumocystis jirovecii</i>	All patients	TMP–SMX	3–6 months
	<i>Candida</i> spp.	Candiduria	Fluconazole	10–14 days
	<i>Aspergillus</i> 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
<i>Pancreas recipients</i>				
Bacteria	<i>Enterobacteriaceae</i> , <i>Enterococcus</i> spp., anaerobes, <i>Staphylococcus</i> spp.	Prolonged and repeated surgery, technical problems affecting the transplant, vascular catheters, undrained collections, duodenal leaks	Piperacillin–tazobactam + Metronidazole	5–7 days
Fungi	<i>Pneumocystis jirovecii</i>	All patients	TMP–SMX	12 months
	<i>Candida</i> spp.	All patients	Fluconazole, echinocandin	14 days
	<i>Aspergillus</i> 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
<i>Intestinal recipients</i>				
Bacteria	<i>Enterobacteriaceae</i> , <i>Enterococcus</i> spp., anaerobes, <i>Staphylococcus</i> 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	<i>Pneumocystis jirovecii</i>	All patients	TMP–SMX	6–12 months
	<i>Candida</i> spp.	All patients	Fluconazole, echinocandin	4 weeks
	<i>Aspergillus</i> 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	Risk factors	Prophylaxis	Duration
<i>Liver recipients</i>			
Bacteria	<i>Enterobacteriaceae</i> , <i>Enterococcus</i> spp., <i>Staphylococcus</i> spp.	Cefuroxime or Piperacillin-tazobactam	48–72 h (keep as short as possible)
Fungi	<i>Pneumocystis jirovecii</i>	TMP-SMX	3–6 months
	<i>Candida</i> spp.	Echinocandin followed by Fluconazole	2–4 weeks
	<i>Aspergillus</i> spp.	Aerosolized Amphotericin B, mold active azole*** (voriconazole, posaconazole or isavuconazole)	4–6 weeks
Virus	CMV	Valganciclovir*	3–6 months
	HSV/VZV	Valacyclovir**	3 months
<i>Lung recipients</i>			
Bacteria	<i>Enterobacteriaceae</i> , <i>Pseudomonas</i> spp., <i>Burkholderia</i> spp., <i>Staphylococcus</i> spp.	Cefuroxime, adapt to recipient and donor bronchial cultures	5–7 days
Fungi	<i>Pneumocystis jirovecii</i>	TMP-SMX	12 months, lifelong****
	<i>Aspergillus</i> spp.	Aerosolized Amphotericin B, Voriconazole	4–6 weeks, lifelong****
Viruses	CMV	Valganciclovir	3–6 months
	HSV, VZV	Valacyclovir**	3 months
<i>Heart recipients</i>			
Bacteria	<i>Enterobacteriaceae</i> , <i>Staphylococcus</i> spp.	Cefuroxime or cefazolin	48–72 h (keep as short as possible)
Fungi	<i>Pneumocystis jirovecii</i>	TMP-SMX	12 months
	<i>Aspergillus</i>	Aerosolized amphotericin B, voriconazole	4–6 weeks
Viruses	CMV	Valganciclovir	3–6 months
	HSV, VZV	Valacyclovir**	3 months
Parasites	<i>Toxoplasma</i>	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, <i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Neisseria</i> , <i>Haemophilus</i> spp. Diffuse interstitial infiltrates: infection (<i>Pneumocystis jirovecii</i> , respiratory viruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus), graft rejection, lung edema, pulmonary hemorrhage, ARDS ^a Nodular infiltrates: bacteria, <i>Aspergillus</i> 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						
<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> Gram-negative bacilli <i>Listeria monocytogenes</i>	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
<i>Mycobacterium tuberculosis</i>	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 <i>Mycobacterium tuberculosis</i> complex	QuantiferON-TB	Pulmonary samples Brain biopsy
<i>Nocardia spp.</i>	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						
<i>Herpes simplex virus</i>	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	–
<i>Varicella zoster virus</i>	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)
<i>Cytomegalovirus</i>	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						
<i>Aspergillus and other molds</i>	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
<i>Toxoplasma gondii</i>	Altered mental status Focal signs ± fever ± seizure	Variable	Abscess(es)	PCR <i>Toxoplasma gondii</i>	PCR	Pulmonary samples + brain biopsy

Table 3 (continued)

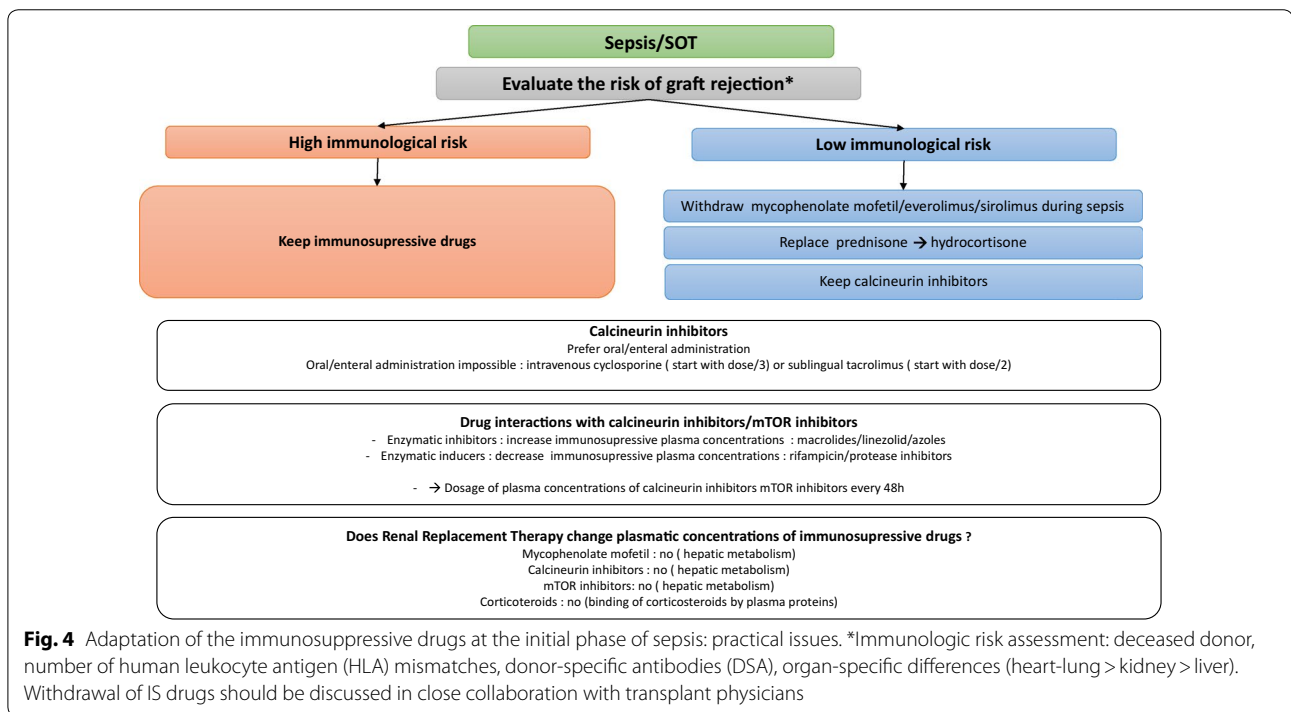
Pathogen	Clinical picture	CSF findings	Brain imaging	CSF samples	Blood samples	Other samples
<i>Cryptococcus neoformans</i>	Sub-acute onset Altered mental status \pm fever	Pleocytosis (100–1000/mm ³) Lymphocytes High Pt; low Glu	Normal Cryptococcoma	India ink stain and culture Cryptococcal antigen PCR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



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 bacteria [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	Modular ^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	<i>Candida</i>	<i>Aspergillus</i>	<i>Pneumocystis</i>	Mucorales
Other rare pathogens to consider	<i>Cryptococcus</i> (late after SOT, particularly in renal tx; possible disseminated also to CNS) <i>Histoplasma</i> (very rare < 1%; endemic areas, community outbreaks)	Consider other molds (<i>Mucorales</i> , <i>Fusarium</i>) <i>Cryptococcus</i> (see left) <i>Histoplasma</i> (see left; frequently disseminated)	Aspecific presentation of other IFD, usually other types of lung lesions coexist	
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, Tetrphase, 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 (Biomérieux, 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.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 23 February 2019 Accepted: 6 March 2019

Published online: 25 March 2019

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