Risk Assessment of Infections in SOT Recipients

2

Mario Fernández-Ruiz and Nicole M. Theodoropoulos

2.1 Introduction

When evaluating a solid organ transplant (SOT) recipient for infection, there are a large number of factors that should be considered. Since these patients are immunosuppressed, they often do not express the same signs and symptoms as a fully immune competent host. For instance, pulmonary infections may not present with cough or shortness of breath. Often, patients may not have fever or leukocytosis with infection. Skin and soft tissue infections may not have all the typical signs of erythema, induration, tenderness, and warmth.

On the other hand, the occurrence of certain opportunistic infections, especially those due to polyomaviruses or herpesviruses, may act as an indicator that the patient is over immunosuppressed. The functional impact on the host's response of the most commonly used immunosuppressive drugs is quite heterogeneous across patients. Unfortunately, there is no gold standard to assessing how immunosuppressed a given patient is. The amount of time that has elapsed since the transplant surgery is also critical in assessing the types of infections a patient is most at risk for. Usually, the longer the time from transplant, the less immunosuppressed a SOT recipient is, but this is not the case in patients suffering from graft rejection episodes requiring enhanced immunosuppression. Surgical complications and anatomical alterations from surgery need to be considered. Making a diagnosis, instead of empirically treating, is

M. Fernández-Ruiz (✉)
Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Instituto de Investigación Sanitaria Hospital "12 de Octubre" (imas12), School of Medicine, Universidad Complutense, Madrid, Spain

N. M. Theodoropoulos
Division of Infectious Diseases and Immunology, University of Massachusetts Medical School, UMass Memorial Medical Center, Worcester, MA, USA

O. Manuel, M. G. Ison (eds.), *Infectious Diseases in Solid-Organ Transplant Recipients*, https://doi.org/10.1007/978-3-030-15394-6_2

critically important in post-transplant patients, as the differential diagnoses may be broad. Invasive procedures and biopsies are often necessary to narrow on a definitive diagnosis.

2.2 Time from Transplant

Since many organ transplant recipients receive induction therapy at the time of transplant, their immunosuppression is often at its peak within a month from transplant. The deleterious effects of these induction therapies—specifically those including T-cell-depleting agents (e.g., polyclonal antithymocyte globulins or the anti-CD52 monoclonal antibody alemtuzumab)—on the cell-mediated immunity have been reported to last up to 1–2 years post-transplant [1, 2]. The more time that passes from transplant, the lower the risk for rejection and often maintenance immunosuppression medications are tapered.

As discussed in Chap. 1, early infections (i.e., those occurring within the first post-transplant month) are typically related to surgery or are donor-derived. Sometimes these events are related to an infection already active before the transplant procedure. The intermediate period (i.e., months 1 through 6 post-transplant) tends to be the time of highest immunosuppression when most opportunistic infections are seen. The typical timeline of infections is altered by the use of antimicrobial prophylaxis and by periods of augmented immunosuppression [3, 4]. Donor-derived infections usually present early after transplant but can be detected up to 1 or more years post-transplant in some cases. Any unknown infection within 6-month post-transplant should involve a look at donor factors and a review of the other recipients of organs from the donor.

2.3 Pre-transplant Recipient Factors

When evaluating a post-transplant patient for infection early after transplant, a review of their pre-transplant history is important, especially noting any history of infections or colonization with fungi or drug-resistant organisms, their pre-transplant serologies, vaccination status, and history of comorbidities. Patients with a history of uncontrolled diabetes mellitus, autoimmune disease or splenectomy, or chronic malnutrition have a unique increased risk for infection [3]. Special evaluation of issues with previous infection or colonization of the system requiring transplant is important. For example, many lung transplant recipients will have prior respiratory infections or colonization and will, therefore, be at risk for recurrence of these infections post-transplant, especially in the case of cystic fibrosis patients.

2.3.1 Donor Factors

Donor infectious disease screening test results need to be reviewed. Most providers understand that recipients that are seronegative for cytomegalovirus (CMV) or

Epstein-Barr virus (EBV) who receive a seropositive donor organ are at high risk for infectious complications from these viruses. However, the impact of donor/recipient serological mismatch for other pathogens such as *Toxoplasma gondii* or the remaining herpesviruses is less characterized. For instance, toxoplasmosis has been reported to be transmitted from donor to recipient after heart transplantation but also occasionally in other transplant populations [5–7].

Additionally, some organ procurement organizations screen deceased donors for West Nile virus, human T-lymphotropic virus-1/2, *Strongyloides stercoralis*, and Chagas (*Trypanosoma cruzi*) antibodies [8]. These test results need to be interpreted and acted on by the recipient transplant teams when appropriate. Donor blood, urine, and sputum are sent for culture at the time of procurement, and results of these cultures are reported several days later. These should be checked as a routine but also in the case of evaluation of a recipient for an early post-transplant infection. Detailed discussion about donor-derived infections will be included in Chap. 3.

2.3.2 Surgical Factors

With the transplant surgery, many details need to be understood by the physicians taking care of the transplant recipient as they can increase risk of infection. The type of anastomosis is essential to understand [9]. Anastomoses that involve bowel place the patient at risk for leakage and peritonitis. Some centers perform pancreas transplants with vesicular anastomoses, and this increases the risk of cystitis. Lung transplant patients are at risk for ischemia at the site of their tracheal anastomosis, and this can increase the risk of fungal and bacterial infections at this site.

Intra-abdominal surgeries are sometimes complicated by splenic injury and subsequent splenectomies. This will increase the risk of severe infections with encapsulated bacteria in the recipient. Other factors that will increase the risk of infection, especially fungal infection in liver transplant recipients, are return to the operating room, need for renal replacement therapy, and large intraoperational volume blood loss [10, 11].

Stents are sometimes placed in the ureter or biliary system in kidney and liver transplant operations, respectively. These foreign bodies need to be assessed and possibly removed earlier than planned when infections arise in these areas post-transplant.

2.4 Post-transplant Factors

In addition to pre-transplant and surgery-related factors, the susceptibility to infection among SOT recipients is modulated by a number of post-transplant variables that must be taken into account in the risk assessment process. Of note, most of them have a dynamic behavior that justifies continuous monitoring throughout the post-transplant period (in particular during the first 12 months).

2.4.1 Community and Healthcare-Associated Exposures

Causative agents of post-transplant infection may be endogenous in nature (posing the risk of reactivation of a latent infection), derived from the donor or the preservation fluid and transmitted through the graft itself or acquired from an exogenous source (through environmental, vector, or human-to-human exposure). Overall, the latter group represents the most usual mechanism of infection during the entire life span of SOT recipients.

Environmental pathogens to which these patients are particularly susceptible comprise of bacteria (*Pseudomonas aeruginosa*, *Legionella* spp.) and both ubiquitous (e.g., *Aspergillus* spp., *Cryptococcus* spp.) and geographically restricted fungi (e.g., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, or *Coccidioides immitis*) [12, 13]. Gardening activities and exposure to potting mixes and compost-derived products are associated with infections due to *L. longbeachae* and dematiaceous (dark-pigmented) fungi [14, 15]. *Listeria monocytogenes* constitutes the most relevant foodborne pathogen in the SOT population [16], although *Salmonella* spp., *Vibrio* spp., or *Cryptosporidium* spp. must be also borne in mind [17]. The incidence of vector-borne infection may be theoretically considered comparable to that of the immunocompetent host. Nevertheless, it has been reported that post-transplant immunosuppression contributes to increase the severity of certain diseases such as babesiosis, ehrlichiosis, or rickettsiosis. Human-to-human transmission can result from direct contact with an infected person or indirectly through an intermediate object. *Mycobacterium tuberculosis* and respiratory viruses (e.g., influenza virus, adenoviruses, or respiratory syncytial virus) are relevant pathogens transmitted from infected individuals, usually but not exclusively in the community setting. Varicella-zoster virus (VZV) is also transmitted by direct contact, droplets or aerosols from vesicular lesions, or respiratory tract secretions.

Healthcare-associated exposure deserves particular attention, since SOT recipients usually have longer hospital and ICU stays, have more requirements for invasive diagnostic and therapeutic procedures, and are more commonly exposed to broad-spectrum antibiotics than other patient groups. Thus, the incidence of healthcare-associated and nosocomial bacterial infection is increased, as is the causative role of multidrug (MDR) Gram-negative bacilli (such as extended-spectrum β-lactamases [ESBL]-producing or carbapenem-resistant *Enterobacteriaceae*), methicillin-resistant *Staphylococcus aureus*, or vancomycin-resistant *Enterococcus*. The frequent use of indwelling devices (e.g., intravascular or urinary catheters or biliary stents) poses an additional risk of biofilm-associated infections. Antibiotic exposure and other factors (e.g., use of proton pump inhibitors or post-transplant hypogammaglobulinemia) explain the particular susceptibility of SOT recipients to *Clostridium difficile* infection, which may entail particularly deleterious effects on graft outcome [17].

2.4.2 Net State of Immunosuppression

Coined by Fishman, the concept of "net state of immunosuppression" refers to the additive measure of factors contributing to the individual susceptibility to infection

Table 2.1 Factors contributing to the "net state of immunosuppression" in SOT recipients (modified from Fishman [18])

Induction therapy (use of T-cell-depleting agents, cumulative dose)
Maintenance immunosuppressive therapy (regimen type, temporal sequence, dose, duration)
Prior immunosuppressive (e.g., chemotherapy) or antimicrobial therapies
Pre-transplant underlying immunodeficiency (e.g., adrenal insufficiency, systemic lupus, complement deficiencies)
Peri-transplant life-support procedures (e.g., vasoactive drugs, renal replacement therapy, invasive mechanical ventilation, ECMO)
Administration of blood-derived products
Disruption of mucocutaneous barrier (e.g., intravenous and urinary catheters, surgical procedures)
Metabolic conditions (e.g., uremia, malnutrition, diabetes, alcoholism, cirrhosis, vitamin D deficiency)
Cytopenias (drug-induced neutropenia or lymphopenia)[a]
Post-transplant de novo hypogammaglobulinemia
Chronic or latent viral infections (CMV, hepatitis B and C, EBV)

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *ECMO* extracorporeal membrane oxygenation
[a]Typically due to mycophenolate mofetil, azathioprine, (val)ganciclovir, or trimethoprim-sulfamethoxazole

in each SOT recipient [18]. It results from the combination of a number of factors, including the nature, dose, and duration of immunosuppressive therapy, the use of invasive life-support techniques, the evolution of graft function, or the deleterious effect on the host's immune response of chronic or latent viral infections, among others (Table 2.1). In addition, the surgical issues related to the transplant procedure contribute to fluid leaks (blood, lymph, urine) and collections, as well as devitalized tissues at the surgical site.

Due to its multifaceted nature and dynamic course, the measurement of the net state of immunosuppression constitutes a clinical and methodological challenge, and it is unlikely that a single biomarker could accurately account for the multiplicity of immune and nonimmune factors involved. The ultimate would be to define a quantitative measure conceptually similar to the area under the curve, which would encompass the multiple contributing variables at a given point. At the present time, therapeutic drug monitoring (TDM) of immunosuppressive agents constitutes the most widely used approach to the immune status in SOT recipients. However, TDM is limited by its unidimensional nature, which does not take into account the synergistic effect of multidrug regimens or the impact of induction therapies with monoclonal or polyclonal antibodies, resulting in a relatively poor correlation with clinical events.

2.4.3 Strategies for Immune Monitoring

From a clinical perspective, the strategies for the immune monitoring in the setting of SOT may be categorized into nonpathogen-specific or pathogen-specific [19]. The first of these approaches evaluates the functionality of a given arm of

the immune system by means of assays (or biological parameters) with no antigen specificity. The nature of the biomarker used, in turn, may be quantitative (e.g., concentration of serum immunoglobulins or complement factors) or provide a functional assessment (e.g., intra-lymphocytic release of adenosine triphosphate [ATP] upon stimulation with phytohemagglutinin [PHA]) (Table 2.2). On the contrary, the pathogen-specific immune monitoring strategies are based on antigen-specific assays that estimate the magnitude and functionality of adaptive immune responses generated by T-cells or B-cells against a defined pathogen. Most of them measure the production of Th_1 effector cytokines (usually interferon [IFN]-γ) after stimulation with a known viral antigen (individual peptide, peptide library, whole virus lysate, or infected dendritic cells). Although there have been progresses in the assessment of specific immunity against VZV, EBV, or polyomavirus BK, the only currently approved assays for clinical use are aimed at measuring CMV-specific cell-mediated immune responses (Table 2.3) [20]. There are different clinical scenarios in which this approach has been clinically explored and that would constitute preferential applications of CMV-specific immune monitoring (Table 2.4) [21]. However, interventional studies based on these nonpathogen-specific or pathogen-specific immune assays are still scarce [22].

2.4.4 Antimicrobial Prophylaxis

As expected, the administration of antimicrobial prophylaxis modulates the incidence and timing of infectious complications in SOT recipients and must be taken into account in the risk assessment. The high efficacy exhibited by certain regimens, such as trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia (PCP) or (val)ganciclovir for CMV, renders very unlikely the occurrence of breakthrough infection while on prophylaxis and modifies the conventional scheme proposed for infection according to the post-transplant period (early, intermediate, and late). Therefore, the period at risk would be displaced to a later phase, once prophylaxis has been discontinued, posing the potential for delayed diagnosis due to low clinical suspicion or diminished awareness [23]. It should be also noted that the impact of some prophylactic strategies is not limited to the primarily targeted pathogen. For instance, anti-CMV prophylaxis with (val)ganciclovir has been proven to be effective in preventing herpes simplex virus (HSV) and VZV reactivation [24], whereas the use of trimethoprim-sulfamethoxazole prophylaxis reduces, in addition to PCP, the incidence of listeriosis, urinary tract infection (UTI), or staphylococcal infection (although appears to have minor effect on the risk of nocardiosis). On the other hand, caveats of current prophylaxis practices include the development of atypical forms of disease (e.g., extrapulmonary *Pneumocystis* infection in patients receiving inhaled pentamidine) or the emergence of antimicrobial resistance (e.g., quinolone-resistant uropathogens or azole-resistant *Aspergillus calidoustus* associated with the widespread use of ciprofloxacin and voriconazole prophylaxis, respectively [25, 26]).

Table 2.2 Summary of methods for nonpathogen-specific immune monitoring (modified from Fernández-Ruiz et al. [19])

Characteristic	Serum immunoglobulins	Serum complement factors	Peripheral blood lymphocyte subpopulations	Soluble CD30	EBV or TTV viremia	iATP in $CD4^+$ T-cells	QuantiFERON-monitor
Required sample	Serum	Serum	Whole blood	Serum	Whole blood, PBMCs, or serum	Whole blood	Whole blood
Assay	Nephelometry	Nephelometry or ELISA (C3, C4, MBL)	Flow cytometry	ELISA	Quantitative PCR	Quantification of iATP release in PHA-stimulated $CD4^+$ T-cells	Quantification of IFN-γ release upon stimulation with anti-CD3 and R848
Functional analysis	No	No	No	Yes	Yes	Yes	Yes
Advantages	Economical and easy to perform. Potential for replacement therapy with IVIG	Economical and easy to perform. Potential for genotyping of *mbl2* gene variants	Easy to perform (automatized methods)	Easy to perform. Commercial assay. Low volume (25 μL) of serum required	Comprehensive assessment of the T-cell response	Only FDA-approved commercial assay (ImmuKnow® assay, Cylex, Columbia, MD). Highly standardized. Large volume of studies	Joint assessment of both innate and adaptive immunity. Commercial test (QuantiFERON-Monitor®; Qiagen, Hilden, Germany)
Disadvantages	Lack of standardized cutoff values. No information on the functionality of the humoral response	Lack of standardized cutoff values. No information on the functionality of the complement system	Lack of standardized cutoff values. No information on the functionality of the cellular response	Only few studies on predicting infection with discordant findings	Only preliminary studies. Lack of technical standardization. Potentially biased by antiviral prophylaxis (EBV)	Only modest PPV and NPV in studies to date. Relatively high cost. Potentially biased by sample storage time	Only preliminary studies

EBV Epstein-Barr virus, *ELISA* enzyme-linked immunosorbent assay, *FDA* Food and Drug Administration, *iATP* intracellular adenosine triphosphate, *IFN-γ* interferon γ, *IVIG* intravenous immunoglobulins, *MBL* mannose-binding lectin, *NPV* negative predictive value, *PBMCs* peripheral blood mononuclear cells, *PCR* polymerase chain reaction, *PHA* phytohemagglutinin, *PPV* positive predictive value, *TTV* Torque Teno virus

Table 2.3 Summary of methods for monitoring of CMV-specific T-cell-mediated immune response (modified from Fernández-Ruiz et al. [19])

Characteristic	MHC-tetramer staining	Intracellular cytokine staining	ELISpot	QuantiFERON-CMV
Required sample (volume)	PBMCs (0.5–1 mL)	PBMCs or whole blood (1–2 mL)	PBMCs (10 mL)	Whole blood (3–5 mL)
Turnaround time	1–2 h	8–10 h	24–48 h	24 h
Antigen	Individual peptide (pp65, IE-1, pp50)	Individual peptide/peptide library/whole virus lysate/ CMV (VR-1814)-infected immature dendritic cells	Individual peptide/peptide library/whole virus lysate/ CMV (VR-1814)-infected immature dendritic cells	Pool of 22 different peptides mapped within pp65, pp50, IE-1, IE-2, and gB
Functional analysis	No (unless associated with intracellular cytokine staining)	Yes	Yes	Yes
Phenotypic characterization	Yes	Yes	No	No
Differentiation between $CD8^+$ and $CD4^+$ responses	Yes	Yes	No	No (detects mostly $CD8^+$ T-cells)
Required knowledge on epitope	Yes	No	No	No
Required knowledge on individual HLA-type	Yes	No	No	No
Commercially available test	CE-approved test recently commercialized (Dextramer CMV® Kit; Immudex ApS, Copenhagen, Denmark)	No	CE-approved commercialized (T-Track CMV®; Lophius Biosciences, Regensburg, Germany)	CE-approved test with increasing clinical experience (QuantiFERON-CMV®; Qiagen, Hilden, Germany)

Table 2.3 (continued)

Characteristic	MHC-tetramer staining	Intracellular cytokine staining	ELISpot	QuantiFERON-CMV
Advantages	High specificity. Short turnaround time	Gold standard. Most existing literature based on this technique. Potential for freeze PBMCs and ship to reference laboratory for testing	Potential for freeze PBMCs and ship to reference laboratory for testing	Simple to perform and highly standardized
Limitations	Labor intensive. Lack of technical standardization. Need for purified PBMCs and access to a flow cytometer	Labor intensive. Lack of technical standardization. No commercial test. Need for access to flow cytometer	Lack of technical standardization. No defined cutoff values. Need for purified PBMCs and access to an ELISpot reader. No differentiation between $CD8^+$ and $CD4^+$ responses	Not differentiation between $CD8^+$ and $CD4^+$ T-cells. Sensitive to lymphopenia (high rate of indeterminate results in patients treated with ATG). Limited to widespread HLA types

ATG antithymocyte globulin, *CE Conformité Européenne*, *CMV* cytomegalovirus, *ELISpot* enzyme-linked immunosorbent spot assay, *HLA* human leukocyte antigen, *MHC* major histocompatibility complex, *PBMCs* peripheral blood mononuclear cells

2.4.5 Antirejection Therapy

The treatment for acute graft rejection may substantially modify the expected timetable of post-transplant infection, since it augments the overall amount of immunosuppression over a short period of time. In addition to the increase in the daily dose of those drugs contained in the maintenance immunosuppression regimen, antirejection therapy usually comprises the administration of steroid boluses, T-cell-depleting agents (e.g., polyclonal antithymocyte globulins) or, in the case of antibody-mediated rejection, agents targeting the B-cell (rituximab). These therapies are frequently associated with the development of lymphopenia (mostly affecting $CD4^+$ T-cell counts) and hypogammaglobulinemia. Recent developments in the approach to steroid-resistant forms of antibody-mediated rejection also include the use of eculizumab (a recombinant humanized monoclonal antibody that targets complement protein C5 and prevents the formation of the terminal membrane attack complex)

Table 2.4 Scenarios with available clinical information supporting the monitoring of CMV-specific T-cell-mediated immune response after SOT (modified from Fernández-Ruiz et al. [19])

Clinical scenario	Predicted event	Monitoring method	Proposed intervention
High-risk patients (D^+/R^-, T-cell-depleting antibodies, lung transplantation) during antiviral prophylaxis	Late-onset disease[a]	QuantiFERON-CMV, ELISpot	Prolong antiviral prophylaxis or close monitoring for viremia if inadequate response
High-risk patients (D^+/R^-) after discontinuing antiviral prophylaxis	Late-onset disease[a]	QuantiFERON-CMV	Prolong antiviral prophylaxis or close monitoring for viremia if inadequate response
Pre-transplant assessment in intermediate-risk patients (R^+ with no other factors)	Post-transplant viremia and/or disease	QuantiFERON-CMV, ELISpot	Initiate antiviral prophylaxis in patients with inadequate response
Intermediate-risk patients (R^+) on preemptive therapy with no concurrent viremia	Subsequent viremia and/or disease	ICS, QuantiFERON-CMV, ELISpot, MHC-tetramer staining	Reduce the frequency and/or discontinue monitoring of viremia if adequate response
Intermediate-risk patients (R^+) on preemptive therapy with asymptomatic viremia	Spontaneous clearance	QuantiFERON-CMV	Withhold antiviral therapy if adequate response
Active CMV infection or disease after discontinuation of antiviral treatment	Post-treatment relapse	ICS	Initiate secondary prophylaxis if inadequate response

CMV cytomegalovirus, *ELISpot* enzyme-linked immunosorbent spot assay, *ICS* intracellular cytokine staining, *MHC* major histocompatibility complex

[a]Refers to the occurrence of CMV disease after discontinuing antiviral prophylaxis with (val) ganciclovir

and bortezomib (a proteasome inhibitor), which increase the risk of neisserial infection and HSV and VZV reactivation, respectively. It should be noted the late-onset rejection usually takes place once antimicrobial prophylaxis has been discontinued, thus rendering the patient particularly susceptible to opportunistic infection [27].

References

1. Peleg AY, Husain S, Kwak EJ, Silveira FP, Ndirangu M, Tran J, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. Clin Infect Dis. 2007;44(2):204–12.
2. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. Clin Infect Dis. 2009;48(6):772–86.
3. Green M. Introduction: infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):3–8.
4. Fishman JA, Practice ASTIDCo. Introduction: infection in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S3–6.

5. Morris MI, Fischer SA, Ison MG. Infections transmitted by transplantation. Infect Dis Clin N Am. 2010;24(2):497–514.
6. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. Am J Transplant. 2011;11(6):1123–30.
7. Wolfe C, Wilk A, Tlusty S, Sifri C, Morris M, Mehta A, et al. Donor-derived toxoplasmosis in solid organ transplant 2008–2015: Opportunities for improvement [Abstract]. Am J Transplant. 2016;16(Suppl 3):736.
8. Fischer SA, Lu K, Practice ASTIDCo. Screening of donor and recipient in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):9–21.
9. Kumar D, Humar A. The AST handbook of transplant infections. Chichester: Blackwell Publishing; 2011.
10. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(5):503–35.
11. Silveira FP, Kusne S, Practice ASTIDCo. Candida infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):220–7.
12. Assi M, Martin S, Wheat LJ, Hage C, Freifeld A, Avery R, et al. Histoplasmosis after solid organ transplant. Clin Infect Dis. 2013;57(11):1542–9.
13. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101–11.
14. Singh N, Chang FY, Gayowski T, Marino IR. Infections due to dematiaceous fungi in organ transplant recipients: case report and review. Clin Infect Dis. 1997;24(3):369–74.
15. Wright AJ, Humar A, Gourishankar S, Bernard K, Kumar D. Severe Legionnaire's disease caused by Legionella longbeachae in a long-term renal transplant patient: the importance of safe living strategies after transplantation. Transpl Infect Dis. 2012;14(4):E30–3.
16. Kruszyna T, Walsh M, Peltekian K, Molinari M. Early invasive Listeria monocytogenes infection after orthotopic liver transplantation: case report and review of the literature. Liver Transpl. 2008;14(1):88–91.
17. Aulagnon F, Scemla A, DeWolf S, Legendre C, Zuber J. Diarrhea after kidney transplantation: a new look at a frequent symptom. Transplantation. 2014;98(8):806–16.
18. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357(25): 2601–14.
19. Fernandez-Ruiz M, Kumar D, Humar A. Clinical immune-monitoring strategies for predicting infection risk in solid organ transplantation. Clin Transl Immunology. 2014;3(2):e12.
20. Egli A, Humar A, Kumar D. State-of-the-art monitoring of cytomegalovirus-specific cell-mediated immunity after organ transplant: a primer for the clinician. Clin Infect Dis. 2012;55(12):1678–89.
21. Torre-Cisneros J, Aguado JM, Caston JJ, Almenar L, Alonso A, Cantisan S, et al. Management of cytomegalovirus infection in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transplant Rev. 2016;30(3):119–43.
22. Ravaioli M, Neri F, Lazzarotto T, Bertuzzo VR, Di Gioia P, Stacchini G, et al. Immunosuppression modifications based on an immune response assay: results of a randomized, controlled trial. Transplantation. 2015;99(8):1625–32.
23. Iriart X, Challan Belval T, Fillaux J, Esposito L, Lavergne RA, Cardeau-Desangles I, et al. Risk factors of pneumocystis pneumonia in solid organ recipients in the era of the common use of posttransplantation prophylaxis. Am J Transplant. 2015;15(1):190–9.
24. Martin-Gandul C, Stampf S, Hequet D, Mueller NJ, Cusini A, van Delden C, et al. Preventive strategies against cytomegalovirus and incidence of alpha-herpesvirus infections in solid organ transplant recipients: a nationwide cohort study. Am J Transplant. 2017;17(7):1813–22.
25. Egli A, Fuller J, Humar A, Lien D, Weinkauf J, Nador R, et al. Emergence of Aspergillus calidoustus infection in the era of posttransplantation azole prophylaxis. Transplantation. 2012;94(4):403–10.

26. Origuen J, Fernandez-Ruiz M, Lopez-Medrano F, Ruiz-Merlo T, Gonzalez E, Morales JM, et al. Progressive increase of resistance in Enterobacteriaceae urinary isolates from kidney transplant recipients over the past decade: narrowing of the therapeutic options. Transpl Infect Dis. 2016;18(4):575–84.
27. Perez-Ordono L, Hoyo I, Sanclemente G, Ricart MJ, Cofan F, Perez-Villa F, et al. Late-onset Pneumocystis jirovecii pneumonia in solid organ transplant recipients. Transpl Infect Dis. 2014;16(2):324–8.