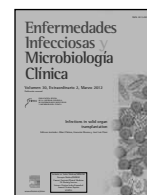




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Infection prevention in solid organ transplantation

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ABSTRACT

Keywords:
Aspergillus
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As complications from infection are a major cause of morbidity and mortality following transplantation, infection prevention is a cornerstone of any modern solid organ transplantation program. There is no doubt that, among other measures, antimicrobial prophylaxis has decreased the incidence and severity of post-transplant infections, and it is a major contributor to the currently improved survival rates of solid organ transplant recipients. This chapter is not a thorough analysis of all studies examining the prevention of infection following organ transplantation, but a practical guide to widely accepted recommendations regarding the prevention of common infections in the transplant setting, such as bacterial infections, including tuberculosis, cytomegalovirus, hepatitis viruses or invasive fungal infections.

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Palabras clave:
Aspergillus
 Citomegalovirus
 Infección
 Prevención
 Trasplante

Prevención de la infección en el trasplante de órgano sólido

RESUMEN

Debido a que las complicaciones infecciosas son una causa importante de morbilidad tras el trasplante, la prevención de la infección es fundamental en cualquier programa moderno de trasplante de órgano sólido. No hay duda de que, entre otros factores, la profilaxis antimicrobiana ha descendido la incidencia y la gravedad de las infecciones posteriores al trasplante y de que contribuye de forma importante a las actuales tasas mejoradas de supervivencia de los receptores de trasplante de órgano sólido. Este capítulo no es un análisis meticuloso de todos los estudios sobre prevención de la infección tras el trasplante de órgano, sino una guía práctica de las recomendaciones ampliamente aceptadas en relación con la prevención de las infecciones más frecuentes en el proceso del trasplante, como son las infecciones bacterianas como tuberculosis, citomegalovirus, hepatitis o infecciones fúngicas invasivas.

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Introduction

As infectious complications are a major cause of morbidity and mortality following transplantation, prevention of infection is a cornerstone of any modern solid organ transplantation program.¹ There is no doubt that, among other measures, antimicrobial prophylaxis has decreased the incidence and severity of post-transplant infections, and it is a major contributor to the currently improved survival rates of solid organ transplant recipients.^{1,2}

Prevention of complications from infection begins with proper screening for the presence of acute or chronic infections in both

donor and recipient before transplantation, followed by a myriad of post-surgical procedures which, in most cases, involves the administration of antimicrobial drugs. Three different preventive strategies are used: vaccination, prophylaxis and pre-emptive therapy. Vaccination involves administering the whole, or a part of, a pathogen to stimulate the recipient's immune system; prophylaxis is the administration of an antimicrobial drug to avoid infection, which may be administered either to all transplant recipients (universal prophylaxis) or to only a subset who are at the highest risk (targeted prophylaxis); pre-emptive therapy is the administration of an antimicrobial drug to recipients who are known to be infected but who are still asymptomatic. Pre-emptive therapy requires sensitive and accurate testing to detect infected recipients who are asymptomatic. Table 1 shows recommendations regarding vaccination for solid organ transplant candidates and recipients.³

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Table 1
Guidelines for vaccination of solid organ transplant candidates and recipients

Vaccine	Before transplant	After transplant
Influenza (I)	Yes	Yes (every year)
Hepatitis B	Yes	Yes
Hepatitis A	Yes	Yes (if HAV seronegative)
Tetanus	Yes	Yes (if no booster in the last 10 years)
Pertussis	Yes	Yes (above all in patients in contact with infants)
Polio (I)	Yes	Yes
Diphtheria	Yes	Yes
<i>S. pneumoniae</i> (P)	Yes	Yes (once after 3-5 years)
Varicella (LA)	Yes	No
HPV	Yes	Yes
Rotavirus, Measles, Mumps, Rubella,	Yes (in children or non-vaccinated adults)	No
<i>V. cholerae</i> *	Yes	Yes
Yellow Fever*	Yes	No
<i>S. typhi</i> (I)*	Yes	Yes
Japanese encephalitis*	Yes	No

HPV: human papilloma virus; I: inactivated vaccine; LA: live attenuated vaccine; P: polysaccharide vaccine.

*Travel vaccine.

The timeline of post-transplant infections (Fig. 1) reflects the relationship between the recipient's epidemiological exposure and the net state of immunosuppression, which is mainly determined by the doses, duration and sequences of immunosuppressive therapies. The timeline is used to establish a differential diagnosis for infection at various stages after transplantation, and also to establish an

adequate infection prevention program, as a specific antimicrobial prophylaxis is used for a specific infection.

Strategies to Reduce Epidemiological Exposure in Transplant Patients

The current goal of transplantation is to offer the transplant recipient a life as healthy and normal as possible. As the risk of infection is always present, in addition to the above-mentioned specific measures, there are a myriad of strategies for safe living. This section deals with infection exposures that transplant recipients face in daily life, with instructions on how to reduce epidemiological exposures.⁴

Recommendations

1. Frequent and thorough hand washing is imperative (AIII).
2. Gloves should be used when heavily contaminated material, such as soil or moss, is handled (during gardening, farming, etc.) Going barefoot should be avoided (CIII).
3. Transplant patients should avoid intravenous drug use, piercing and tattoos.
4. Avoid tobacco smoke. Smoking and exposure to environmental tobacco smoke are risk factors for bacterial and community-acquired viral infections (CIII). Marijuana smoking should also be avoided because of its association with exposure to fungal spores from *Aspergillus* spp. and other organisms (BIII).
5. Transplant patients should avoid contact with persons who have respiratory illnesses (AIII), and if it is not possible to avoid contact, patients should wear a surgical mask (CIII).
6. If possible, transplant recipients should avoid occupational hazards related to the risk of tuberculosis exposure (prisons, shelters and some health-care facilities) and other infectious risks (animal care settings, construction, gardening or farming).
7. Construction sites, excavations or extremely dusty places are not recommended for transplant recipients.

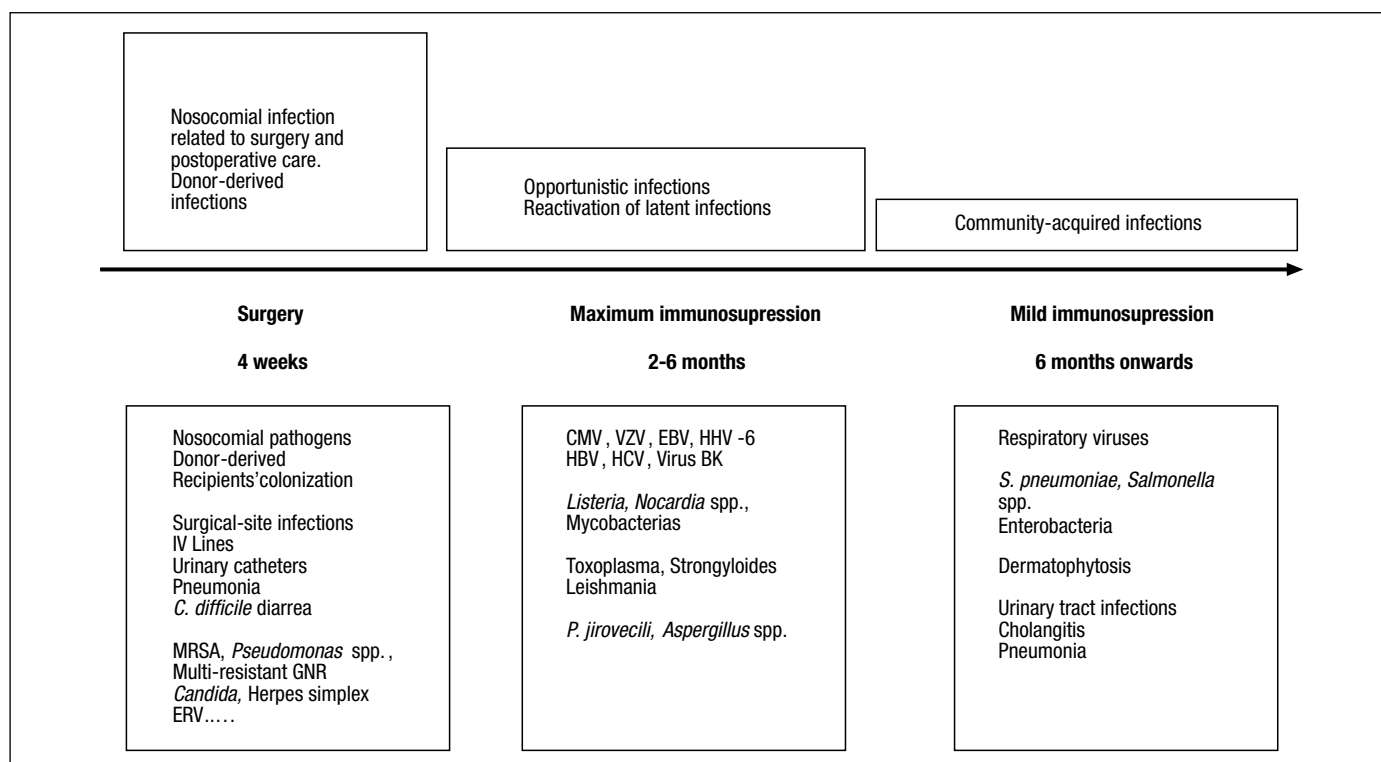


Figure 1. The timeline of post-transplant infections. The height of the bars expresses the relative number of infections in each period.

CMV: cytomegalovirus; EBV: Epstein-Barr virus; GNR: gram negative rods; HBV: hepatitis B virus; HCV: hepatitis C virus; HHV-6: human herpesvirus 6; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *Enterococcus* spp.; VZV: varicella-zoster virus.

8. Transplant patients should neither drink from lakes, rivers or public fountains (cryptosporidiosis, giardiasis and bacterial pathogens) (AIII), nor swim in water that is likely to be contaminated (BII). Drinking tap water while travelling in countries with poor sanitation should be avoided.

9. Transplant patients should avoid eating raw eggs, meat, fish, seafood and poultry to prevent food-borne diseases.

10. Transplant patients should balance the benefits of pet ownership with the risks of transmission of infection. Maintenance of pet health is crucial (BIII).

11. Transplant patients should practice safe sex.

12. The potential infection hazards in the workplace must be considered when evaluating the risk of potential exposures to fungal spores or respiratory viruses in relation to the post-transplant timeline.

Bacterial Infection

Prophylactic measures immediately before and after surgery are specifically aimed at preventing bacterial infections. The administration of perioperative antibacterial prophylaxis is recommended to reduce the incidence of infection at the surgical site. Moreover, to prevent the onset of disease from antibiotic-resistant bacteria, appropriate measures should be taken to control infection (hand hygiene, contact isolation, antibiotic policy, etc.).

Selective bowel decontamination

In liver transplant programs and, to a lesser extent, in pancreas-kidney, lung and intestine transplant programs, selective bowel decontamination (SBD) is used to prevent early bacterial infection after transplantation. SBD aims to reduce the intestinal aerobic bacterial load (while maintaining anaerobic flora) in order to prevent bacterial translocation. Absorbable or non-absorbable oral antibiotics may be employed for this purpose. The most common non-absorbable oral antibiotic regimens use aminoglycoside (gentamicin, tobramycin or neomycin), colistin and vancomycin, and an antifungal agent (nystatin or amphotericin B). However, recent studies question the effectiveness of SBD in solid organ transplants (SOT) (AI).^{5,6}

Clostridium difficile^{7,8}

In addition to infection control measures, prevention of *Clostridium difficile* infection (CDI) must focus on reducing the risk factors for developing the disease in patients who acquire *C. difficile*.

Recommendations

1. Minimize the frequency and duration of antimicrobial therapy and the number of antimicrobial agents prescribed to reduce CDI risk (AII).

2. Limit antimicrobial use through formulary restrictions and/or antimicrobial stewardship programs to reduce the incidence of CDI (AII).

3. Other modifiable risk factors for the development of CDI, such as gastric acid suppression or prolonged hospitalization, should be reduced if possible (CIII).

4. Use a combination of strict hand hygiene and contact precautions to significantly reduce the incidence of CDI (BII).

5. 10% bleach solutions are sporicidal and may be used for environmental decontamination during outbreaks (BII).

Nocardia spp.

The incorporation of routine prophylaxis with cotrimoxazole, which is effective in preventing *Pneumocystis jiroveci* infection at the usual dose of 160 mg of trimethoprim and 800 mg of sulfamethoxazole

three times a week, may be insufficient to prevent nocardiosis in solid organ transplant patients (CII).

Listeria monocytogenes

Infection due to *Listeria monocytogenes* is usually a late opportunistic infection occurring after transplantation. It is uncommon in organ transplant patients due in part to the widespread use of cotrimoxazole prophylaxis (BII)

Tuberculosis

Tuberculosis (TB) is a particularly important condition in solid-organ transplant recipients due to treatment delays caused by the difficulties involved in diagnosis, and because of the pharmacological toxicity associated with treatment. In solid organ transplant recipients, TB usually develops from a site of latent infection in the recipient.^{9,10}

Recommendations for treatment of latent TB infection

1. Treatment for latent TB infection should be administered to patients on transplant waiting lists or to recipients who have ≥ 1 of the following conditions: 1) a PPD skin test (initial or after a booster effect) with a ≥ 5 mm induration; 2) a history of untreated TB; or 3) a history of contact with a patient with active TB (AII).

2. Patients with chest radiograph findings compatible with untreated TB (apical fibronodular lesions, calcified solitary nodules, calcified lymph nodes or pleural thickening) should also receive therapy for latent TB infection (AII).

3. Before initiation of treatment for latent TB infection, patients should undergo a thorough evaluation to rule out active TB.

4. The drug of choice for treatment of latent TB infection is isoniazid (300 mg/day) supplemented with vitamin B₆ for 9 months (AI).

5. Ideally, latent TB infection should be treated before transplantation, except possibly in the case of liver transplantation. If treatment cannot be completed before the procedure, it should be completed after the procedure. The duration and dose of isoniazid therapy are the same, irrespective of whether it is administered before or after transplantation. Patients who have completed therapy before transplantation do not need to repeat it after the procedure.

6. Tolerance to isoniazid is generally good; however, the possibility of isoniazid-induced hepatotoxicity is possible in these patients. Treatment of latent TB infection must be suspended if aspartate aminotransferase or alanine aminotransferase values increase 3-fold in patients with symptoms or 5-fold in patients with no accompanying symptoms.

7. When it is necessary to suspend treatment for latent TB infection because of toxicity, the patient should be closely monitored and treatment should be completed with drugs other than isoniazid. However, this should only be done in patients with a high risk of TB, such as those who recently had a positive PPD result after having had a negative result.

8. Alternatives to isoniazid include rifampicin (with or without isoniazid) for 4 months (BII) or rifampicin and pyrazinamide for 2 months (CIII); however, the latter combination has been associated with severe liver toxicity and is generally not recommended (except when prophylaxis must be completed within a short period of time) and must always be administered under expert supervision. This regimen is not recommended for patients with previous liver disease, consumers of alcohol, or patients who have developed isoniazid-induced hepatotoxicity. For patients at high risk of TB, some authors recommended treatment with levofloxacin and ethambutol for at least 6 months (BIII).

9. The regimens that include rifampicin are only recommended for pre-transplantation treatment of latent TB infection due to the medication interactions that affect this drug.

Table 2

Summary of specific recommendations for the prevention of CMV in solid organ transplantation

Type of organ	D+/R-	Other situations
Liver	PPX: Valganciclovir (900 mg/d) for 3–6 months (AIII); or i.v. ganciclovir (5 mg/kg/d) (AI) followed by PT up to 3 months after end of PPX (AII); or PT: Valganciclovir (900 mg/12 h) for 14 days, checking negativization of viremia and monitoring every 1–2 weeks during the first 3 months (AII).	In R+ patients, either PPX (valganciclovir, 900 mg/d 3 months (BII), or i.v. ganciclovir, 5 mg/kg/d (AI), followed by valganciclovir, 900 mg/d) or PT with valganciclovir, 900 mg/12 h (AII), or i.v. ganciclovir, 5 mg/kg/12 h (AI), for 14 days and subsequent monitoring.
Kidney	PPX: valganciclovir (900 mg/d) (AI) for 6 months post-transplant (AI) Alternatives: oral valaciclovir (2 g/6 h) (AI), or i.v. ganciclovir (5 mg/kg/d) (if not tolerated orally), for a maximum of 3 months post-transplant (AI).	In R+ patients, PT is recommended with valganciclovir (900 mg/12 h) or i.v. ganciclovir (5 mg/kg/12 h) for 14–21 days and monitoring (BI). Alternative: PPX with valganciclovir (900 mg/d), valaciclovir (2 g/6 h) or i.v. ganciclovir for 3 months (AII). Patients receiving induction with anti-lymphocyte antibodies (except basiliximab) or exhibiting steroid-resistant rejection must receive ganciclovir (5 mg/kg/day) for at least 14 days (BI) or valganciclovir (900 mg/d) for 3 months (CIII).
Heart	PPX: valganciclovir (900 mg/d) or i.v. ganciclovir (5 mg/kg/d) for 3–6 months (AI). Anti-CMV gammaglobulin in association with i.v. ganciclovir may benefit high-risk patients (BII).	In R+ patients: PPX or PT. Monitoring of CMV in non-prophylaxis patients. If monitoring results are positive, i.v. ganciclovir (5 mg/kg/12 h) or valganciclovir (900 mg/12 h) for 2–4 weeks (BII). Exclude hypogammaglobulinemia in patients with relapsing CMV disease (BIII). PPX: i.v. ganciclovir (5 mg/kg/12 h) until tolerated orally and then valganciclovir (900 mg/d) until month six (AII). In the case of treatment with anti-lymphocyte antibodies or steroids at doses above 10 mg/kg/day, valganciclovir must be administered (900 mg/d) for a maximum of 3 months (BIII).
Lung	PPX: i.v. ganciclovir (5 mg/kg/12 h) until tolerated orally and then valganciclovir (900 mg/d) for 6–12 months (AII). Anti-CMV gammaglobulin in association with i.v. ganciclovir may benefit high-risk patients (BII). At the end of PPX, monitor patients and start PT with valganciclovir (900 mg/12 h) or i.v. ganciclovir (5 mg/kg/12 h IV) (AII).	In R+ patients: PPX i.v. ganciclovir (5 mg/kg/12 h) until tolerated orally and then valganciclovir (900 mg/d) until month 6 (AII). In case of treatment with anti-lymphocyte antibodies or steroids at doses above 10 mg/kg/day, treatment with valganciclovir must be restarted at doses of 900 mg/day for a maximum of 3 months (BIII).
Pancreas and Kidney/Pancreas	PPX: valganciclovir (900 mg/12 h) for 3 months (CII). In the presence of other associated risk factors consider increasing prophylaxis to 6 months (CIII). Then, PT with valganciclovir (900 mg/12 h) or i.v. ganciclovir (5 mg/kg/12 h) (CIII).	In R+ patients who have not received anti-lymphocyte antibodies or high doses of steroids as rejection treatment, pre-emptive therapy is recommended (CIII) with valganciclovir (900 mg/12 h) or i.v. ganciclovir (5 mg/kg/12 h). In patients receiving anti-lymphocyte antibodies for more than 3 days or presenting cortico-resistant rejection, start prophylaxis with i.v. ganciclovir or valganciclovir for 1–3 months (CIII).
Small bowel	PPX: i.v. ganciclovir (5 mg/kg/12 h) or valganciclovir (900 mg/d) for a minimum of 6 months; treatment may be prolonged until lymphocyte counts = CD4+ >200 cells/ml (CIII).	In R+ patients, PPX with i.v. ganciclovir (5 mg/kg/day) or valganciclovir (900 mg/day) for between 3 and 6 months post-transplant (CIII). In patients receiving anti-lymphocyte antibodies or presenting cortico-resistant rejection, start prophylaxis with i.v. ganciclovir or valganciclovir for between 1 and 3 months (CIII).

Recommended doses of antiviral agents for normal renal function (creatinine clearance >70 ml/min) and neutrophil counts >1000/1-l.

D+/R-: positive donor/negative recipient; i.v.: intravenous; R+: positive recipient; PPX: universal prophylaxis; PT: pre-emptive treatment.

10. Liver transplant recipients present special problems when they receive treatment for latent TB infection because of the high risk of hepatotoxicity. Some authors recommended delaying the administration of treatment until after transplantation when liver function is stable (BIII). The benefit of treating latent TB infection in liver recipients is clearer when there are risk factors, such as a recent change in PPD results from negative to positive, a history of incorrectly treated TB, direct contact with an untreated person with TB, residual TB lesions on the chest radiograph and added immunosuppression.

Viral Infections

Prevention of viral infections through vaccination is covered in Table 1. The following focuses on prevention of viral infections through prophylaxis or pre-emptive therapy.

Cytomegalovirus

Cytomegalovirus is a major cause of morbidity in solid organ transplant recipients. More than 85% of transplant recipients in Spain

are infected by CMV before transplantation, and without preventive measures, most of them will develop reactivation of the infection (CMV infection), with one third showing clinical symptoms (CMV disease) during the first three months after transplantation.

Current guidelines for the prevention of CMV infection following solid organ transplantation are based on three factors: 1) Pre-transplant donor and recipient CMV serology (the combination of a seronegative recipient with a seropositive donor at the highest risk of developing CMV disease, a D+/R- situation); 2) The use of certain immunosuppressive drugs (i.e. the use of antilymphocyte drugs or steroid “boluses”); and 3) the type of organ (the highest risk is associated with small-bowel, lung and pancreas transplantation), recently updated by GESITRA-REIPI-SEIMC.¹¹

Recommendations

1. Prophylaxis and pre-emptive therapy have been shown to be useful tools in the prevention of CMV following solid organ transplantation (AI).

2. Most experts recommend the use of prophylaxis in all types of transplants in the D+/R- situation, with additional pre-emptive

Table 3

Prevention of invasive fungal infections in solid organ transplant recipients

Type of Transplant	Target population	Antifungal drug	Duration
Liver	High-risk liver transplant recipients: 1) hemodialysis, retransplantation, fulminant hepatic failure; or 2) Cr CL<50 ml/min, >40 transfusion blood products, Y de Roux, >3 + survey cultures <i>Candida</i> spp., re-exploration after transplantation	Caspofungin (BII); Lip-AB 3 mg/kg IV (BII); micafungin (CIII); or anidulafungin (CIII)	Determined by the presence of risk factors
Pancreas	All	Fluconazole (BII);	1-2 weeks
Intestinal	All	fluconazole (BII);	3-4 weeks
	High-risk pancreas or intestinal transplant recipients: Acute rejection and poor initial allograft function, hemodialysis, laparotomy after transplantation, bacterial or CMV co-infection, anastomotic problems, overimmunosuppression	Lip-AB 3 mg/kg IV (CIII); caspofungin (CIII); micafungin (CIII); or anidulafungin (CIII)	Determined by the presence of risk factors
Kidney	No prophylaxis (DIII)		
Heart	High-risk heart transplant recipients: Acute rejection hemodialysis, re-exploration after transplantation, CMV disease, excessive <i>Aspergillus</i> spp. air colonization	Itraconazole; voriconazole; posaconazole or equinocandins (CIII)	3 months or more, Determined by the presence of risk factors
Lung	All	Nebulized lip-AB B 25 mg Nebulized amphotericin B lipid complex 50 mg Three times weekly until resolution of bronchial suture Once a week from 2 to 6 months Voriconazole 200 mg/12 h O	Lip-AB once every two weeks Amphotericin B lipid complex once a week Indefinite or for a minimum of 12 months 4 months minimum, determined by the presence of risk factors
Not lung or kidney SOT	High-risk late invasive aspergillosis Chronic rejection, allograft dysfunction due to VHC (liver transplant), hemodialysis, overimmunosuppression	Nebulized lip-AB B 25 mg Nebulized amphotericin B lipid complex 50 mg Initially, three times weekly	Lip-AB once every two weeks Amphotericin B lipid complex once-a-week Determined by the presence of risk factors

therapy during the first 3-6 months following the discontinuation of prophylaxis to avoid late-onset CMV disease (CIII).

3. In small-bowel, lung and pancreas transplantation, whether the recipient is seropositive or seronegative, prophylaxis is always preferred. Pre-emptive treatment cannot be recommended because the first diagnosed infection may be serious, such as pneumonitis or intestinal disease (intestinal SOT) (BII).

4. In liver, heart and kidney seropositive recipients, pre-emptive therapy is preferred (BII), but only if proper CMV monitoring, in both an inpatient and outpatient setting, is warranted. If prophylaxis is elected, it extends to 3 months in liver, heart, pancreas and kidney transplants (AII).

5. The duration of prophylaxis in the D+/R- situation is 3-6 months, depending on the type of organ and immunosuppressive therapy (AI).

6. In lung transplantation, the duration of CMV prophylaxis extends from 6-12 months (AII) and in small-bowel transplantation to a minimum of 6 months or longer if the CD4 lymphocyte count is less than 200/mm³.

7. Patients who receive therapy with antilymphocyte drugs (ATG, ALG or OKT3) or alemtuzumab but not basiliximab (AI), and those who receive steroid "boluses" as treatment for acute rejection episodes (CIII) should receive prophylaxis (1-3 months).

8. In D-/R- situations, leukocyte-depleted blood products and products from seronegative donors can be used.

9. See Table 2 for specific recommendations.

Other herpesviruses

There is no specific recommendation for the systematic prevention of herpes simplex virus, HHV-6 or HHV-8 infection in solid organ transplantation.

Epstein-Barr virus

Epstein-Barr virus (EBV) is associated with the majority of post-transplant lymphoproliferative disorders (PTLD). As occurs with CMV, EBV seronegative recipients of grafts from seropositive donors are at the highest risk of developing PTLD. Given the absence of reliable effective therapy for PTLD, it would be advisable to prevent it; however, there is currently no universally accepted strategy.¹²

Recommendations

1. Data regarding the use of antiviral drugs (acyclovir or ganciclovir) does not support their universal use in the prevention of EBV-associated PTLD (AII). There is some evidence to support the use of ganciclovir/valganciclovir in the D+/R- situation in kidney transplant patients (BII).

2. There are some data to support the use of a pre-emptive approach by monitoring EBV viral load in high-risk patients and the use of antiviral drugs and rituximab (a monoclonal B cell antibody), together with a decrease in immunosuppressive therapy (BIII).

Varicella-zoster virus

Regarding prevention of varicella-zoster virus (VZV), there is no data to support the long-term use of antivirals to prevent VZV infection after solid organ transplantation. Nevertheless, there are specific recommendations for VZV seronegative recipients.¹³

Recommendations

1. Varicella vaccination with the live attenuated vaccine is indicated at least 2-4 weeks before transplantation in VZV seronegative recipients (AII).

2. VZV seronegative recipients should receive post-exposure prophylaxis (AI). Administration of VZV immune globulin should be made as soon as possible, within the first 96 hours after exposure is indicated (AII). Co-administration of antivirals (acyclovir, valacyclovir, ganciclovir) during 10-21 days with specific immunoglobulin is supported by some experts (CIII).

Hepatitis B virus

We should distinguish between prevention of HBV following liver vs. non-liver transplantation. In liver transplantation, HBV infection is the cause of end-stage liver disease and the objective is to prevent graft reinfection.¹⁴

Recommendations

Liver transplantation

1. For HBsAg+ recipients, the regimen of choice is a life-long combination of hepatitis B immunoglobulin (HBIG), initially given intravenously, followed by the IM route in an outpatient setting, along with anti-HBV drugs.

2. In low-risk patients (VHB-DNA negative at the time of transplantation), entecavir or tenofovir are the preferred anti-HBV drugs. Lamivudine may also be used.

3. Discontinuation of HBIG may be considered after 2 years post-transplantation in low-risk patients (VHB-DNA negative at the time of transplantation, fulminant HBV hepatitis, VHD co-infection).

Non-liver transplantation

1. In HBsAg+ non-liver transplant recipients, monotherapy with entecavir or tenofovir is currently the preferred therapy for prevention of HBV reactivation after transplant; however, lamivudine may be used in low-risk patients (VHB-DNA negative).

Influenza

Influenza A and B are a common cause of viral infections in transplant patients each year. In 2009, a novel influenza A virus (H1N1) spread worldwide, causing a new pandemic. This pandemic has highlighted the importance of proper prevention of influenza infection in transplant recipients.¹⁵

Recommendations

1. Transplant recipients, candidates, household contacts and health-care workers caring for transplant patients should receive an annual inactive influenza vaccine.

2. It is recommended that the seasonal influenza vaccine be given 3-6 months after transplantation, as the immune response to early vaccination may be partially protective; however, in an epidemic situation, it is better to perform early vaccination than no vaccination at all.

3. Universal chemoprophylaxis (oseltamivir, zanamivir) is not routinely recommended, but may be considered for recent transplant recipients or those for whom immunization is contraindicated.

4. Post-exposure prophylaxis with antivirals (10 days of oseltamivir or zanamivir) may be considered when a solid organ transplant recipient has had known exposure to a contact infected with influenza. Alternatively, recipients may watch for early signs and symptoms of influenza, at which time they could take specific antiviral drugs.

Fungal Infections

Invasive fungal infections (IFIs)

The absence of clinical trials and the epidemiological differences in IFIs between different transplant programs mean that there are no

definitive recommendations for the prevention of IFI in SOT. The reduction in the incidence of IFIs needs to be analyzed together with other types of measures that may be more important than the use of prophylaxis with antifungals, such as optimization of surgical procedures, the proper handling of immunosuppression and environmental control of certain filamentous fungi. All these measures have been compiled in the recently published 2011 Guidelines SEIMC-GEMICOMED-REIPI.^{16,17} Table 3 reflects these recommendations. Invasive candidiasis is the most frequent infection in liver, pancreas and intestinal recipients, but invasive aspergillosis carries a higher morbidity and mortality and, given that they share risk factors, prevention must be combined. There is a high-risk category of liver, pancreas and intestinal recipients that shares risk factors for invasive candidiasis and aspergillosis in which the antifungal used to prevent IFI must have activity against *Aspergillus* spp.

*Pneumocystis jiroveci*¹⁸

1. There is no precise standard regarding which patients should receive prophylaxis or which is the ideal regimen to follow. Although some authors recommend administering prophylaxis to only the highest-risk patients (patients receiving higher than normal doses of immunosuppressants, with multiple rejections, with CMV infection or graft dysfunction), most transplant teams have opted for universal prophylaxis (BII).

2. For lung and small bowel transplant recipients, as well as any transplant patient with a history of prior PCP infection or chronic CMV disease, universal lifelong prophylaxis may be indicated (AIII).

3. The drug of choice for preventing infection due to *P. jiroveci* is cotrimoxazole (AI), which also prevents infection by *Toxoplasma gondii*, *Listeria monocytogenes*, *Isospora belli*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, community-acquired *Staphylococcus*, *Nocardia asteroides*, and gram-negative aerobic bacteria.

4. The minimum required dose of cotrimoxazole is unclear. Similar efficacy has been shown for regimens ranging from the daily administration of cotrimoxazole 2 or 3 days a week (either on consecutive or alternate days) to 7 consecutive days per month (160 mg of trimethoprim and 800 mg of sulfamethoxazole) (AI).

5. It is recommended that prophylaxis be initiated immediately after transplantation and that it cover the maximum risk period (first 6 months post-transplant) (AII). The occurrence of late cases has led some groups to administer prophylaxis for life or at least to maintain it for the first 12-18 months in high-risk patients or organ transplant patients requiring more than 10 mg of prednisone per day.

Antiparasitics

Toxoplasmosis

Heart and liver transplant patients who receive a seronegative graft from a seropositive donor are considered to be at high risk of developing a primary infection due to *Toxoplasma gondii*.

Recommendations

1. Numerous studies confirm that trimethoprim/sulfamethoxazole (160/800 mg) 3 times weekly is effective and safe, with the added benefit that these drugs simultaneously prevent other diseases such as infection due to *P. jiroveci* (AII).

2. In high-risk patients, some groups administer sulfadiazine (2 g/day) or clindamycin (300-450 mg/8 h) for the first 6-8 weeks, and sometimes maintain treatment with cotrimoxazole for life.

3. The duration of prophylaxis has not yet been clearly determined, as cases of infection after completion of prophylaxis have been reported.

4. In the event that patients have an allergic reaction to sulfonamide or *Clostridium difficile*-associated diarrhea, pyrimethamine (25-50

mg/day) in combination with folinic acid, dapsone (50 mg/day) or atovaquone (750 mg/8-12 h) may be administered.

Leishmaniasis

No specific prophylactic measures have been established. Contact with the vector should be avoided.

Tripanosomiasis

In seropositive patients, the recommended post-transplant procedure is based on the persistent control of serology and parasitemia, with specific treatment of reactivations. There is insufficient data to recommend prophylaxis or "anticipated" treatment.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Fishman JA. Introduction: infection in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S3-S6.
2. Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. *Infect Dis Clin North Am.* 2010;24:273-83.
3. Danzinger-Isakov L, Kumar D. Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant.* 2009;9 Suppl 4:S258-62.
4. Avery RK, Michaels MG. Strategies for safe living following solid organ transplantation. *Am J Transplant.* 2009;9 Suppl 4:S252-7.
5. Gurusamy KS, Kumar Y, Davidson BR. Methods of preventing bacterial sepsis and wound complications for liver transplantation. *Cochrane Database Syst Rev.* 2008;(4):CD006660.
6. Zwaveling JH, Maring JK, Klompmaier IJ, Haagsma EB, Bottema JT, Laseur M, et al. Selective decontamination of the digestive tract to prevent postoperative infection: a randomized placebo-controlled trial in liver transplant patients. *Crit Care Med.* 2002;30:1204-9.
7. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol.* 2010;31:431-55.
8. Dubberke ER, Riddle DJ. *Clostridium difficile* in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S35-40.
9. Aguado JM, Torre-Cisneros J, Fortún J, Benito N, Meije Y, Doblas A, et al. Consensus document for the management of tuberculosis in solid organ transplant recipients. *Enferm Infecc Microbiol Clin.* 2009;27:465-73.
10. Aguado JM, Torre-Cisneros J, Fortún J, Benito N, Meije Y, Doblas A, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis.* 2009;48:1276-84.
11. Torre-Cisneros J, Fariñas MA, Castón JJ, Aguado JM, Cantisán S, Carratalà J, et al. GESITRA-SEIMC/REIPI recommendations for the management of cytomegalovirus infection in solid-organ transplant patients. *Enferm Infecc Microbiol Clin.* 2011;29:735-58.
12. Allen U, Preiksaitis J. Epstein-barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S87-96.
13. Pergam SA, Limaye AP. Varicella zoster virus (VZV) in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S108-15.
14. Levitsky J, Doucette K. Viral hepatitis in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S116-30.
15. Kumar D, Blumberg EA, Danziger-Isakov L, Kotton CN, Halasa NB, Ison MG, et al. Influenza Vaccination in the Organ Transplant Recipient: Review and Summary Recommendations(dagger). *Am J Transplant.* 2011;11:2020-30.
16. Fortún J, Carratalà J, Gavalda J, Lizasoain M, Salavert M, De la Camara R, et al. Guidelines for the treatment of invasive fungal disease by *Aspergillus* spp. and other fungi issued by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). 2011 Update. *Enferm Infecc Microbiol Clin.* 2011;29:435-54.
17. Ruiz-Camps I, Aguado JM, Almirante B, Bouza E, Ferrer-Barbera CF, Len O, et al. Guidelines for the prevention of invasive mould diseases caused by filamentous fungi by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). *Clin Microbiol Infect.* 2011;17 Suppl 2:1-24.
18. Martin SI, Fishman JA. Pneumocystis pneumonia in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S227-33.