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Epidemiology and risk factors of infections after solid organ transplantation

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ABSTRACT

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Infection remains a significant complication after solid organ transplantation (SOT). The incidence of various pathogens varies widely depending on the presence of specific factors, according to which patients can be classified into different risk categories that may merit tailored prophylaxis strategies. Both the endogenous origin of microorganisms (previous colonization or latent infection) and new acquisition (primary infection from donor or environment) should be considered. Bacterial infections predominate in patients with complex hospital stays or anatomical alterations. Viral infections, caused both by opportunistic (CMV, EBV, BKV, etc.) and common viruses (influenza, respiratory virus, VVZ, etc.), are of great importance, and may contribute to chronic rejection. Fungal infections are uncommon nowadays, but cause high mortality and deserve prophylaxis for a subset of patients. Parasitic infections are a clear threat, mainly in transplanted patients or those travelling to endemic areas. Physicians attending SOT recipients should be aware of these risk factors, which include specific host characteristics, type of transplantation, microorganism and immunosuppressive policy.

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Epidemiología y factores de riesgo de infecciones tras trasplante de órgano sólido

RESUMEN

Palabras clave:

CMV
Epidemiología
Infección
Profilaxis
Trasplante de corazón
Trasplante de órgano sólido
Trasplante de páncreas
Trasplante hepático
Trasplante pulmonar
Trasplante renal

La infección sigue siendo una complicación significativa tras el trasplante de órgano sólido (TOS). La incidencia de los diferentes patógenos varía ampliamente dependiendo de la presencia de factores específicos y, de acuerdo con esto, los pacientes pueden clasificarse en diferentes categorías de riesgo que precisarán estrategias profilácticas específicas para cada categoría. Deben tenerse en cuenta tanto los microorganismos de origen endógeno (colonización previa o infección latente) como los de nueva adquisición (infección primaria a partir del donante o del entorno). Las infecciones bacterianas predominan en los pacientes con estancias hospitalarias complejas o alteraciones anatómicas. Las infecciones virales, causadas tanto por virus oportunistas (citomegalovirus, virus de Epstein-Barr, virus BK, etc.) como por virus comunes (influenza, virus respiratorios, virus de la varicela zoster, etc.) son esenciales y pueden contribuir al rechazo crónico del trasplante. Las infecciones fúngicas no son habituales hoy en día, pero provocan una alta mortalidad y precisan profilaxis en un subgrupo de pacientes. Las infecciones parasitarias son una clara amenaza, principalmente en pacientes trasplantados que viajen a zonas endémicas. Los médicos que tratan a los receptores de TOS deben ser conscientes de estos factores de riesgo, que incluyen las características específicas del receptor, tipo de trasplante, microorganismo y planes de inmunosupresión.

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Epidemiology of Infections After Solid Organ Transplantation

The incidence of infection after solid organ transplantation (SOT) is affected by a number of factors: the type of organ transplanted, the level of immunosuppression, the need for additional antirejection therapy and the occurrence of surgical complications, among others.¹ Table 1 shows the incidence of infectious diseases in various types of SOT.²

The sources of infectious agents after transplantation include the recipient (endogenous), the allograft itself and the environment.³

Endogenous source

There are two types of endogenous sources: 1) the SOT recipient's flora that colonizes mucous membranes and skin, and 2) reactivation of a latent infection. The endogenous flora is the most important source of infection especially in the early post-surgical period in patients with prolonged hospitalizations or who require mechanical ventilation. The pathogens involved in these infections include gram-negative bacilli, gram-positive organisms, and *Candida* spp.

Immunosuppression may cause latent pathogens to reactivate, even many years after transplantation (tuberculosis or endemic fungi). Thus, it is important to identify such infections before transplantation in order to develop preventive strategies for these patients. Pathogens that can reactivate after transplantation include: *Mycobacterium tuberculosis*, viral infections (Herpes simplex virus [HSV], varicella zoster virus [VZV], cytomegalovirus [CMV], hepatitis B, hepatitis C, papilloma virus and BK polyomavirus), some parasites (*Strongyloides stercoralis*, *Trypanosoma cruzi*, *Toxoplasma gondii*) and endemic systemic mycoses (*Histoplasma capsulatum*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*).⁴⁻⁷

The donor allograft

Transplanted organs can transmit microorganisms from the donor. The greatest risk in the development of infection is exposure to a donor pathogen when a recipient is at risk for primary infection (absence of pre-existing immunity). The most common manifestation of these risk strata is primary CMV infection, in which this subset has the highest risk of disease and complications.⁸ Transmission of Epstein-Barr virus (EBV) from a seropositive donor to a seronegative recipient increases the risk of post-transplant lymphoproliferative disorder (PTLD).⁹ *T. gondii* has been transmitted by seropositive heart donors, especially in seronegative recipients, but transmission by other organs is rare.¹⁰ Other infections transmitted from donor organ tissues include West Nile virus, lymphocytic choriomeningitis virus, rabies, HIV, hepatitis B and hepatitis C viruses, herpes simplex virus, Chagas disease and tuberculosis.¹¹⁻¹⁵

The environment

Transplant recipients can have contact with a number of potential pathogens within the community. These organisms include common respiratory virus (influenza, parainfluenza, respiratory syncytial [RSV] virus, adenovirus and human metapneumovirus), bacterial pathogens (*Streptococcus pneumoniae*, *Mycoplasma*, *Legionella*, *Mycobacterium tuberculosis*, *Nocardia* spp., *Listeria monocytogenes*, *Salmonella*, *Clostridium difficile*), fungi (*Aspergillus* spp, *Cryptococcus* spp., endemic fungi) and parasites (*T. gondii*). In this setting, post-transplantation patients are counseled regarding measures aimed at avoiding environmental exposure to infection. Patients should avoid contact with people who have colds, influenza, tuberculosis and other contagious infections. Recommendations also include washing fresh fruits and vegetables and cooking all meat and seafood thoroughly. SOT recipients should avoid changing litter boxes and cleaning birdcages. Any plans for travel outside of the United States,

Table 1

Incidence of infectious diseases (%) in solid-organ transplant recipients

Type of infection	Liver	Kidney	Heart	Lung/ heart-lung	Pancreas/ kidney- pancreas
Bacterial	33-68	47	21-30	54	35
Cytomegalovirus	22-29	8-32	9-35	39-41	50
Herpes simplex virus	3-44	53	1-42	10-18	6
Varicella zoster virus	5-10	4-12	1-12	8-15	9
<i>Candida</i> spp.	1-26	2	1-5	10-16	32
Mycelial fungi	2-4	1-2	3-6	3-19	3

Canada or Western Europe should be discussed with the patient's physician prior to departure.²

Infections of Significant Relevance in Transplant Recipients

Etiologies of infection in SOT recipients are diverse, including common community-acquired bacterial and viral diseases and uncommon opportunistic infections typical of immunocompromised hosts. The incidence of opportunistic infections is decreasing in transplant recipients because of improved surgical techniques, the use of prophylaxis, enhanced immunosuppressive regimens and better diagnostic methods.¹

Bacterial infections

Bacterial infections occur in 33% to 54% of SOT recipients.² The types of bacterial infections following solid organ transplantation are partly related to the transplant operation, to the length and severity of hospital stay and to the immunosuppressive treatment.¹⁶

Common bacteria are a significant cause of potential severe infections among transplant recipients. Furthermore, antimicrobial resistance is increasing in immunocompromised hosts and should be considered in antibiotic empirical treatment.^{17,18} The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in USA and causes >64% of all bloodstream infections in some ICUs.¹⁹ In Europe, in contrast, the incidence of MRSA has stabilized, partially due to a lower prevalence of community-acquired MRSA. The incidence of MRSA infection after transplantation is not well known, but varies from one transplant center to other. In a study of infections involving liver transplant recipients in USA, 90% of *S. aureus* isolates were methicillin-resistant.¹⁷ However, MRSA made up 16% of all *S. aureus* isolates of a surveillance study of bloodstream infections in transplant recipients in Spain.²⁰

Multi-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are also increasing as the etiology of infection in SOT recipients, especially in the early post-transplantation period in the nosocomial setting. These multi-drug resistant infections have been associated with poor outcomes.²⁰ Extended-spectrum beta-lactamase producing gram-negative enteric bacilli have been an increasing cause of infection in transplant recipients, accounting for 14% of all bacteremic episodes of SOT recipients in Spain.²⁰

SOT recipients are at increased risk of *Clostridium difficile* infection. Incidence of *C. difficile* infection in this population is estimated to be 1%-31% depending on the type of transplant. Fulminant colitis develops in up to 8% of immunocompetent patients and rises to 13% in SOT recipients with *C. difficile* infection.^{21,22}

The primary source of tuberculosis in SOT recipients is the reactivation of latent *Mycobacterium tuberculosis* infection.²³ In Spain, the incidence of tuberculosis in SOT recipients was 512 cases per 100,000 inhabitants per year, which was higher than that in the general population (19 cases

per 100,000 inhabitants per year).²⁴ Most tuberculosis cases in transplant recipients occur within the first year post-transplantation and although pulmonary forms predominate, the proportion of extrapulmonary infections is much higher than in the general population.²⁵⁻²⁷ Mycobacterial infection may be difficult to treat after transplantation because of interactions between the antimicrobial agents, mainly rifampin and immunosuppressive drugs.²⁸

Nocardia and *Listeria* are uncommon infections related to cellular immunity deficiency in transplant recipients. The most common presentation of *Nocardia* infection is pulmonary disease followed by brain abscess, meningitis and disseminated disease. Risk factors for *Nocardia* disease in SOT recipients are high-dose steroids, history of CMV disease and high levels of calcineurin inhibitors.^{29,30} The most frequent presentation of listeriosis is bacteremia followed by meningoencephalitis. Risk factors for *Listeria* infection in SOT recipients are diabetes mellitus, CMV infection or disease and intake of high-dose steroids. Trimethoprim-sulfamethoxazole prophylaxis, on the other hand, has a protective effect.³¹

Viral infections

Herpes virus group

Following primary infection, long-term cellular and humoral immunity develops, but herpesviruses remain latent within the host. Viral persistence is controlled in the immunocompetent host by the cellular immune system, but immunosuppression following transplantation may lead to viral replication and symptomatic infection. Viruses included in this group are CMV, HSV, VZV, EBV and human herpes virus 6, 7 and 8.

CMV continues to be the major pathogen-affecting SOT. Transplant recipients develop CMV disease either as a primary infection, transmitted by the donor or blood products to a seronegative recipient and as a reactivation or as a reinfection (when donor-transmitted virus is imposed on an endogenous reactivated virus). Primary CMV infection is the most serious in terms of direct clinical disease and outcome. CMV causes direct effects such as CMV syndrome. Tissue invasive disease is the digestive involvement in SOT. However, CMV also has the ability to modulate the immune system producing a variety of indirect effects. These indirect effects include an increased incidence of other opportunistic infections and acute chronic allograft rejection.^{8,9}

Active replication of EBV is present in 20% to 30% of transplant recipients receiving immunosuppressive drugs, and more than 80% in those receiving antilymphocyte-antibody therapies. Although mononucleosis-like syndrome has been described in some patients, the most important effect of EBV is its role in post-transplant proliferative disorder (PTLD).⁹ This disorder is usually a B-cell lymphoproliferative process that ranges from a polyclonal process to a malignant monoclonal lymphoma with a reported mortality of 40%-60%.³²

Other viruses

The BK polyomavirus has been associated in renal allograft with hemorrhagic cystitis, interstitial nephritis and ureteric obstruction.³³⁻³⁸ Adenovirus can cause hemorrhagic cystitis and severe infections in pediatric recipients.³⁹ Parvovirus B19 can cause anemia and myocarditis in SOT recipients.⁴⁰ SOT recipients are at high risk of developing anal human papillomavirus infection and neoplasia.⁴¹ Respiratory viruses are community acquired and can predispose to bacterial infections and graft rejection in lung recipients.^{42,43} HHV8 and HHV6 can also affect SOT recipients.^{44,46}

Fungal infections

The incidence of systemic fungal infections varies with the type of organ transplanted, the immunosuppressive regimen and the incidence of surgical complications, and ranges from 2%-40%.² Most

invasive fungal infections in SOT recipients are caused by *Candida spp* originating from endogenous sources. This can be explained by the compromise of cell-mediated immunity due to the immunosuppressive therapy and the high frequency of conditions that lead to increased *Candida* colonization (antibiotic use, intravenous catheters, surgery, etc.). All of these factors predispose patients to invasive *Candida* infections. *Candida albicans* is the most frequent isolated species, although the incidence of other *Candida* species associated with fluconazole resistance, such as *C. glabrata* or *C. krusei*, is increasing in SOT recipients.^{9,20}

The mean incidence of invasive aspergillosis in SOT recipients is around 1.4%, ranging from 0.2% in renal recipients to 3% in lung recipients. Invasive aspergillosis is associated with a high mortality rate in SOT recipients (<70%).⁴⁷⁻⁵² However, survival appears to have improved in recent reports on advances in early diagnostic methods and the development of new antifungal agents.^{53,54}

Among SOT recipients who are not receiving prophylaxis, *Pneumocystis jirovecii* causes pneumonia in 10% of cases, with a higher incidence in lung recipients. However, *P. jirovecii* disease is rare nowadays in SOT recipients because low-dose trimethoprim-sulfamethoxazole provides excellent prophylaxis.^{9,55}

Parasitic infections

Toxoplasmosis after SOT may develop after reactivation of a latent infection, after allograft transmission in a seronegative toxoplasma recipient or after post-transplantation epidemiological exposure.⁵⁶ The allograft is the main source of infection, especially in heart recipients. Seronegative serostatus before transplantation is the main risk factor for developing toxoplasmosis.^{57,58}

Strongyloides stercoralis is a helminth that can be maintained in the human intestinal tract for decades and can cause disseminated disease in transplant recipients with a mortality rate near 71%.⁵⁹ Patients who have resided in or traveled to an area of endemic infection must have stool specimens samples examined for the presence of this parasite prior to transplantation or should receive empirical therapy.⁶⁰

Timing of Infection Post-Transplantation

There are three post-transplantation time frames during which specific infections most frequently occur. These include the first month, the second through the sixth months and the late post-transplant period (beyond the sixth month).⁶¹ Among the factors that influence this distribution of infections are the different levels of immunosuppression at each moment, the proximity to the surgical procedure and critical care unit stay, the environmental exposures and, of course, the risk of donor-related infections. Retransplantation itself, which involves a more complex surgery and previous immunosuppression, is also a major factor in the relative risk of infection development. The risk of opportunistic infections is considered highest during the first four months after SOT, as we will discuss later.

The aforementioned chronology may be altered in a specific patient, with infections characteristic of any given period occurring simultaneously and with an overall increased severity of infection.⁶² As we mentioned, it should be noted that the epidemiology of infections after transplantation is changing due to the reduced importance of surgery-related infections, thanks to the great efficacy of prophylactic strategies (*P. jirovecii*, *T. gondii* and CMV), the sophistication of immunosuppressive agents and, of course, the significant improvement in diagnostic capabilities.

First month after transplantation

Most infections diagnosed during the first month after transplantation are related to surgical complications, and match

those occurring in similar surgical patients. They include bacterial and candidal wound infections, pneumonia, urinary tract infection, intravascular catheter sepsis, infections of biliary, chest and other drainage catheters and *Clostridium difficile* associated diarrhea.¹

The anatomical site near the surgical area is especially susceptible to early infection. In the first month post-transplantation, renal and pancreatic transplant recipients are at risk for perigraft hematomas, lymphoceles and urinary leaks. Liver transplant recipients are at risk for portal vein thrombosis, hepatic vein occlusion, hepatic artery thrombosis and biliary stricture formation and leaks. Heart transplant recipients are at risk for mediastinitis, and lung transplantation recipients are at risk for disruption of bronchial anastomosis. The only common viral infection during the first month post-transplantation is reactivated herpes simplex virus (HSV) infection in seropositive individuals prior to transplantation.

Chronic or latent donor infections that involve the allograft may be transmitted to the immunosuppressed recipient and become clinically apparent during early periods. Some of these infections include HBV, HCV, tuberculosis, fungal and toxoplasmosis, which are uncommon nowadays.⁹ Although the dose of immunosuppressants administered during this period is higher than in subsequent months, the time available is not enough to make the patient susceptible to infections by opportunistic microorganisms, unless there is a massive exposure⁶³ or an excessive immunosuppression level.

Second to sixth month after transplantation

The period from the second to the sixth month after transplantation is the period when infections “classically” associated with transplantation are manifested.^{1,9,61,62,64} Recipients are deeply immunosuppressed and more severe infections appear. Viral infections are common, mainly CMV infection, although these days it has been diminished due to prophylaxis and preemptive therapy. Other opportunistic pathogens, such as *Aspergillus* species, *Nocardia* species, *Toxoplasma gondii* and *Listeria monocytogenes*, typically occur in this time frame. *Pneumocystis jirovecii*, formerly very common in this period, is now infrequent due to prophylaxis.

In addition, during the 1–6 month interval after transplantation, reactivation of latent microorganisms (*Mycobacterium tuberculosis*, hidden focus of bacterial infection, viral hepatitis) present in the recipient before transplantation may occur. Affected organs may vary for each type of transplant, but the lung predominates in all.

More than six months after transplantation

From 6 months after transplantation onwards, most transplant recipients do relatively well, suffering from the same infections seen in the general community. The rate of opportunistic infections is usually low. These include influenza virus, urinary tract, cholecystitis and pneumococcal pneumonia infections. The only opportunistic viral infection commonly seen during this period is reactivated varicella-zoster virus infection manifesting as herpes zoster.^{1,9,61,62,64}

However, patients who have had frequent episodes of acute rejection requiring augmented immunosuppressive therapy, those with chronic rejection who are maintained at a higher baseline level of immunosuppression and those with chronic renal failure remain at risk for the opportunistic agents more classically seen in the second to sixth months after transplantation (*Cryptococcus neoformans*, CMV, *L. monocytogenes* and *Nocardia* species).

Most infections that occur after the sixth month post-transplantation can be classified into one of the following types: First, infections against which the graft is particularly vulnerable, such as recurrent urinary tract infections in renal transplant patients or chronic or recurrent cholangitis in liver transplant recipients; second, recurrences from previous infections, mainly viral (such as herpes zoster rashes), papovavirus (BK and JC) infections that can

Table 2

Risk factors related to higher risk of infection after transplantation

Host related
Age: older recipients and donors
Underlying disease (diabetes, hepatitis that may persist or recur)
Previous hospital admissions and antimicrobial therapy: higher rate of multi-resistant pathogen colonization
Critical clinical situation before transplantation (mechanical ventilation, ventricular assist devices, etc.)
Renal insufficiency
Poor nutritional status
Previous surgery near the transplant area
Transfusions
Latent infections (tuberculosis, CMV, VZV, Strongyloides, regional mycosis, etc.)
Absence of specific immunity (toxoplasma, CMV, EBV, HSV)
Genetic polymorphisms
Transplant related
Type of transplantation (site of most common infections)
Surgical trauma and related complications
Prolonged surgery and high transfusion requirements
Donor related infections (toxoplasma, Chagas, etc.)
Immunosuppression
Drugs: induction, maintenance and rejection episodes therapy
Immunomodulatory infections: CMV and HCV increase the risk of opportunistic infections

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; VZV: varicella zoster virus.

determine ureteral obstruction, hemorrhagic cystitis and interstitial nephritis, subacute and chronic hepatitis (especially those due to hepatitis C virus), tumors (such as verruca vulgaris) and post-transplant lymphoproliferative syndromes caused by Epstein Barr virus, which is especially prevalent in transplanted children.

Cryptococcal meningitis and some forms of CMV disease, such as retinitis, rarely occur and when they do they frequently appear late after transplantation, usually more than a year after transplantation. It is known that highly effective prophylaxis against CMV is conditioning the occurrence of late CMV disease when it is withdrawn.

Risk Factors for Infection

Solid organ transplant recipients should not be considered a uniform population in terms of risk level for suffering specific types of infection. This risk may vary as time progresses after transplantation, the type and depth of immunosuppression and the degree of exposure to different microorganisms. Accordingly, individual risk factors should be taken into account in order to choose efficacious prophylaxis strategies and empirical therapies at different moments after transplantation. Some of the factors that have been found useful for stratifying the risk of infection are summarized in Table 2. Some will be present in the host or donor before transplantation, while others will be related to the transplantation procedure itself and to subsequent complications.

Host-related factors

Recipient and donor age may increase the risk of infectious complications and exacerbate their consequences.⁶⁵ Recipients' underlying conditions should also be considered. For example, acute

Table 3
Drugs used to prevent or treat rejection after SOT

Agent		Increased risk of infection
Polyclonal antibodies	Antithymocyte globulins	CMV, PTLD
	Anti-human thymocyte immune globulin (rabbit)	
	Lymphocyte immune globulin antithymocyte (equine)	
Monoclonal antibodies	Anti-CD25 (il-2 receptor) antibodies: basiliximab, daclizumab	No
	Anti-CD20 antibody: rituximab	HBV reactivation
	Anti-CD52 antibody: daclizumab	CMV, <i>P. jirovecii</i> , invasive fungal infections
	Anti-CD3 antibody: muromonab-CD3 (OKT3)	CMV, PTLD
Corticosteroids	Prednisone, prednisolone	Corticosteroid free regimens may decrease CMV and HCV recurrence. High doses increase the risk of <i>Listeria</i> , <i>Salmonella</i> , <i>Legionella</i> , micobacteria, <i>Nocardia</i> , <i>Cryptococcus neoformans</i> , <i>Candida</i> , <i>Aspergillus</i> , <i>P. jirovecii</i> , herpesvirus, <i>Toxoplasma gondii</i> and <i>Strongyloides stercoralis</i>
Cytotoxic drugs	Azathioprine	–
	Mycophenolate mofetil	CMV
Anticalcineurinic agents	Cyclosporine, tacrolimus	BK virus
M-tor inhibitors	Rapamycin (sirolimus), Everolimus	Reduced risk of PTLD, and BKV

liver failure as a cause of liver transplantation is related to a higher rate of fungal complications, and so these patients need to receive antifungal prophylaxis. Lung transplant recipients with previous COPD or cystic fibrosis may require a more prolonged stay in the intensive care unit and may be colonized with more resistant pathogens.⁶⁶ Patients receiving immunosuppressive drugs before transplantation in order to control the underlying disease (autoimmune hepatitis, for example) have a higher risk of post-transplant infections and may constitute an indication for perioperative antifungal prophylaxis. The disease leading to the transplantation is also important, since sometimes reoccur (hepatitis B or C) in the allograft, increasing the risk of opportunistic infections. Diabetic renal transplant recipients have an increased risk of urinary tract and soft tissue infections. Finally, other less significant problems present in the recipient before transplantation (diverticulosis, lithiasis, chronic bronchitis) may become a significant problem when immunosuppression is established.

Polymorphisms of innate immunity receptors, especially TLR4 mutation, have been related to higher risk of CMV disease.⁶⁷

The clinical situation before transplantation is also important. Patients awaiting transplantation in the intensive care unit (mainly if intubated or requiring circulatory assist devices or dialysis) are at higher risk of subsequent infection (mainly fungal and bacterial). Prolonged pre-transplant hospital admissions, therapy with antimicrobials or immunosuppressants and poor nutritional status may all be associated with colonization of resistant pathogens.

Finally, it is of the utmost importance to determine if the patient may harbor a pathogen that may be reactivated after transplantation, such as tuberculosis, regional mycoses and *Strongyloides* (travel history, vaccination status, etc.). Risk levels for primary infections (CMV, EBV, *Toxoplasma*, etc.) also need to be established.

Microorganism related

As mentioned before, endogenous microorganisms may cause severe infection after transplantation. Previous colonization with multi-resistant pathogens (MRSA, VRE, ESBL-producing gram negatives, etc.) should be investigated before transplantation, and a decolonization attempt should be performed.^{68,69} Solid organ transplantation is a well-known risk factor for infection after MRSA colonization.⁷⁰ Double kidney-pancreas Tx recipients and those who develop post-transplant urinary obstruction are more frequently infected by multiresistant enteric bacilli.⁷¹ Lung transplant recipients

colonized with certain *Burkholderia* or *Pseudomonas* species are known to have a greater risk for death after transplant; therefore, individual prophylactic regimens are designed for these patients.⁷² These infections are associated with significant morbidity after transplantation.

Fungal infections are not as common as bacterial or viral infections in SOT recipients. However there are specific subsets of patients with significantly higher risk that deserve antifungal prophylaxis. These risk factors include retransplantation or reoperation, renal failure requiring dialysis, CMV disease and post-transplant neoplasia. Liver recipients with very prolonged surgery and/or requiring large amounts of blood products are also at high risk. Finally, early aspergillosis cases are reported in SOT recipients that required very prolonged intubation periods after transplantation.

SOT recipients are at a high risk of acquiring environmental pathogens when a massive exposure occurs. Therefore, in cases of nosocomial outbreaks of *Legionella*, influenza and *Aspergillus*, patients should receive full attention and be provided with early diagnosis. In some cases, universal prophylaxis is warranted considering the high risk and related mortality of these infections.⁵¹

Due to the significant increase in immigration rates (10% of donors and transplant recipients in Spain), international travel and the new phenomenon of “transplant tourism”, emerging tropical infectious diseases should now be considered in this population. Among them Chagas, *Histoplasma capsulatum* and HTLV-I/II are especially relevant.⁷³ Post-solid organ transplantation nucleic acid testing (NAT) testing should be available to diagnose these infections in a timely way.^{74,75}

Immunosuppression related factors

Solid organ recipients require the administration of exogenous immunosuppressive agents in order to avoid rejection. Some of the most commonly used drugs are presented in Table 3. Most patients receive perioperative induction therapy with the intention of eluding cellular rejection while maintaining low levels of calcineurin inhibitors when the risk of toxicity is higher. In the past, prolonged courses of polyclonal antithymocyte globulin (ATG) or monoclonal OKT3 were used, bringing with them high rates of infectious complications, mainly of viral etiology. At present, other agents are preferred, such as the new monoclonal antibodies: daclizumab, alemtuzumab or basiliximab and monoclonal anti-CD20 antibodies (rituximab). These drugs maintain a low rate of rejection with a significantly lower number of infectious complications, when used

mainly for induction therapy. Patients receiving alemtuzumab developed less infections than those treated with basiliximab. Disseminated *Candida* infections were more common in patients receiving alemtuzumab.⁷⁶ When these drugs are used for the treatment of corticosteroid-resistant rejection, the risk of opportunistic infections is significantly higher.^{77,78} In this situation, anti-CMV prophylaxis is recommended.

Most common maintenance regimes include the simultaneous administration of 1) glucocorticoids, 2) anti-proliferative agents (such as azathioprine and mycophenolic acid) or mTOR inhibitors (such as sirolimus and everolimus) and 3) calcineurin inhibitors (such as cyclosporine and tacrolimus).

Corticosteroids inhibit a wide range of immune responses, including inflammatory response, cellular immunity and, to a lesser extent, humoral immunity. Under normal conditions, SOT recipients receive low doses of corticosteroids as maintenance therapy and can be totally withdrawn, particularly in abdominal organ recipients. However, high doses are needed to treat acute rejection episodes. The associated cellular immunosuppression increases the risk of infections caused by *Listeria*, *Salmonella*, *Legionella*, mycobacteria, *Nocardia*, *Cryptococcus neoformans*, *Candida*, *Aspergillus*, *P. jirovecii*, Herpesvirus, *Toxoplasma gondii* and *Strongyloides stercoralis*. Currently, without recent rejection episodes, steroid-related opportunistic infections are not so common.

Calcineurin inhibitors are the backbone of maintenance immunosuppressive therapy in SOT recipients and are usually combined with corticosteroids and mycophenolate mofetil or mTOR inhibitors. Tacrolimus is more potent than cyclosporine and its use is linked to fewer episodes of rejection and infection, probably due to the diminished requirement for corticosteroids and antilymphocyte agents, both of which may cause nephrotoxicity and hypertension. CyA is also related to gingival hyperplasia, hirsutism and hyperlipemia, while tacrolimus causes more diabetes and neurologic toxicity. Both drugs are controlled by measuring serum levels. When the levels exceed intended limits, a higher risk of CMV reactivation should be considered.

The new m-Tor inhibitor sirolimus is not associated with higher rates of infection;⁷⁹ however, it may cause interstitial pneumonitis.⁸⁰ Therapy with m-TOR inhibitors decreases the incidence of cytomegalovirus infection, BKV and probably PTLT. However, coadministration with calcineurin inhibitors requires careful dose adjustment to prevent renal toxicity. Its use may impair the response to some vaccines, such as the pandemic influenza A H1N1 vaccine.

As mentioned earlier, the excess immunosuppression required to treat acute rejection episodes (mostly when they prove resistant to glucocorticosteroids) significantly increases the risk of opportunistic infections, such as CMV. Chronic allograft dysfunction usually requires retransplantation and is also associated with a higher susceptibility to infectious complications.

Factors that depend on the type of transplant

Despite the similarities mentioned, the predominant type of infection, the severity of the illness and even death rates vary widely in relation to the transplanted organ. Overall, renal transplant patients have fewer infectious complications (0.98 episodes per patient), while pancreas, intestine and lung transplant recipients are the most affected (3.1 episodes per patient). Liver transplant recipients have more bacteremias, usually of intra-abdominal origin, while 75% of heart-lung recipients suffer severe lung infections.⁹

Renal Transplant

Urinary tract infection is the most common bacterial infection occurring in renal transplant recipients, particularly in the first months post-transplant.⁸¹ Fungi and viruses can also cause urinary tract

infections, but infections caused by these organisms are less common than those caused by bacteria. Both the lower and upper urinary tract (encompassing grafted or native kidneys) can be affected. The major risk factors for urinary tract infection in renal transplant recipients include indwelling bladder catheters, handling and trauma to the kidney and ureter during surgery, anatomic abnormalities of native or transplanted kidneys (such as vesicoureteral reflux, stones and stents), neurogenic bladders (especially in diabetic patients) and possible rejection and immunosuppression. In addition, urinary tract infection is a relatively frequent cause of bacteremia.^{82,83}

The presence of asymptomatic bacteriuria is a common finding in these patients and their management has not yet been clarified. Its presence is not associated with renal function impairment but increases the risk of pyelonephritis and bacteremia. Virtually all renal transplant centers systematically investigate the presence of bacteriuria and many treat it, even in patients with no associated clinical manifestations. Today, the actual utility of this measure remains unknown.

The typical microorganisms causing post-transplant urinary tract infections are the enteric gram-negative bacilli and enterococci. In addition, *Corynebacterium urealyticum* (group D2) has been recognized as a potential pathogen in this population.⁸⁴ This observation is clinically important because *C. urealyticum* is difficult to isolate and is not sensitive to conventional oral antibiotics. Complicated infections are more common among transplant recipients with prolonged anuria, such as dialysis patients.

The morbidity associated with urinary tract infections appears to be related to the timing of episodes after transplantation. Infections occurring in the hospital are more serious, with bacteremia occurring in approximately 10 percent and graft infection in 90 percent of recipients. These infections may be associated with allograft dysfunction and may predispose to development of acute rejection. The clinical presentation of early post-transplantation urinary tract infection is variable. Some patients are asymptomatic whereas others present with fever, chills and graft pain and tenderness. Allograft dysfunction can also occur in this setting. The idea that urinary tract infections detected in the first 6 weeks should receive long-term treatment is not currently supported, and antimicrobial management should be similar to other patients. However, it is essential to note that these patients have frequently previous antibiotic therapy. Therefore, the possibility of having multi-resistant pathogens, including infections that come from the community, is very high. The use of long-term antimicrobial prophylaxis is controversial, as it may increase the likelihood of infectious organisms developing resistance to treatment.

Renal transplant recipients and patients with terminal renal failure are at much greater risk than the general population of suffering *Mycobacterium tuberculosis* infection. It is therefore essential that one consider this possibility in the differential diagnosis and know the patient's pre-transplant PPD and epidemiological history. As with other solid organ transplant recipients, renal transplant patients may suffer infections linked to cellular immunosuppression (*L. monocytogenes*, *N. asteroides*, *Cryptococcus neoformans*, *P. jirovecii*) between 2 to 6 months after transplantation. CMV infection is much less frequent and severe in these patients than in other transplant recipients. It should however be included in the differential diagnosis if renal function deterioration occurs. Like all transplant patients, kidney graft recipients may be frequently infected by the varicella-zoster virus (VZV) or by the JC virus, which causes progressive multifocal leukoencephalopathy. The presence of late BK virus infection is however much more characteristic of this group, which frequently leads to graft failure.⁸⁵

Liver Transplant

Bacterial intra-abdominal infections (abscesses, intrahepatic and extrahepatic cholangitis and peritonitis) are characteristic of liver

transplants recipients. Many of these complications require surgery in addition to antimicrobial treatment, as they may be related to complications of bile duct sutures or hepatic artery thrombosis. It is therefore advisable to perform a radiological examination (Doppler ultrasound, CT scan) of the abdominal cavity in all liver transplant recipients with fever or bacteremia of no obvious origin. Cholangitis causes fever and jaundice but may present without right upper quadrant pain, and therefore may go unnoticed. The diagnosis of cholangitis requires a study of the biliary tract in search of stenosis or obstruction. After the initial ultrasound, endoscopic cholangiography or magnetic resonance cholangiography are the techniques of choice.^{86,87}

Although the overall incidence of fungal infections in liver transplant recipients has declined due to early treatment of high-risk patients (fulminant hepatitis, multiple transfusions, renal failure, reoperation, bile duct-jejunum anastomosis), the overall mortality rate remains high, particularly for invasive candidiasis and aspergillosis, and therefore patients often receive prophylaxis during the first month.⁸⁸

Pancreas Transplant

Pancreas transplantation is usually performed in conjunction with renal transplantation. Its main indication is the treatment of end stage renal disease associated with type 1 diabetes. These patients require a high level of immunosuppression to prevent rejection and therefore have a high rate of infections. Infections are mainly located in the abdominal cavity and urinary tract when pancreatic secretions drain into the urinary bladder. Diarrhea due to *C. difficile* is also common. Risk factors for intra-abdominal infection are: age over 40 years, enteric drainage, organs donated by living relatives and kidney transplantation after simultaneous kidney-pancreas transplantation. *S. aureus* is the most common pathogen, followed by *Enterococcus* spp. and enterobacteria. Recurrent *Candida* urinary tract infections are frequent.⁸⁹

Heart Transplant

Infections are the leading cause of death in the first year after heart transplantation. Nearly half of heart transplant recipients experience significant infection during the first year post-transplantation. Cardiac transplant patients have an overall incidence of infection ranging from 30%-60%, with a related mortality of 4%-15%. Bacterial infections predominate (43%-60%), followed by viral (40%-45%) and to a lesser extent, fungal and protozoal (8%-14%) complications.

Early-onset infections occur in critical care units, and are caused by nosocomial organisms. They usually involve the lung and mediastinum, whereas late-onset infections have a more varied etiology and preferentially affect the lung, skin and genitourinary tract. Pneumonia is the most common bacterial infection. In the first month after transplantation, the main etiologic agents are *P. aeruginosa*, *A. baumannii*, Enterobacteriaceae, *L. pneumophila* and *S. aureus*. After the first month post-transplant, community pathogens such as *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Legionella* spp., or opportunistic bacteria such as *M. tuberculosis*, *N. asteroides* and *R. equi* are the main microorganisms that cause pneumonia.⁹⁰

Specific to this group of patients are post-surgical mediastinitis and infections associated with circulatory assist devices that can be used as bridges to transplantation or in situations of severe ventricular dysfunction. Mediastinitis is usually caused by *S. aureus* or *S. epidermidis*, although negative bacilli may be involved. When cultures are negative, the presence of *Legionella*, *Mycoplasma hominis* and *Mycobacteria* needs to be excluded. Mediastinitis needs to be considered in heart transplant recipients with bacteremia of unclear source within the first month after transplantation.⁹¹ Endocarditis is rare.

Heart transplant patients are also particularly susceptible to developing toxoplasmosis when negative recipients receives hearts

from positive donors, because the heart is a muscle that can spread infection more easily than other organs.

Lung Transplant

Lung transplant recipients have increased susceptibility to infection due to the lung's direct communication with the environment. Losses of some mechanical defense mechanisms, such as the removal of the cough reflex below the tracheal or bronchial anastomosis and the alteration of mucociliary clearance, also favor the emergence of infections. On average, lung transplant recipients experience 3 episodes of infectious complications, and the type of infection depends on the clinical setting of the transplanted patient (e.g., harvest injury, complication from primary disease, airflow obstruction from chronic airway rejection). Therefore, awareness of the clinical setting enhances diagnostic accuracy. Many of these patients arrive at transplantation colonized by bacteria and/or multi-resistant fungi. The native lung can contain microorganisms that can be transmitted to the transplanted lung.⁹²⁻⁹⁴

Pneumonia and tracheobronchitis are the most frequent infections, especially in the first weeks after transplantation. Overall, Gram-negative bacteria predominate, but in patients with cystic fibrosis, the main pathogens are *P. aeruginosa*, *B. cepacia*, *Aspergillus* and *Scedosporium* spp. Pneumonia after 3-6 months after transplantation is a manifestation of bronchiolitis obliterans in the graft and in this case Gram-negative bacteria are the main cause. Lung transplant recipients may experience tracheobronchitis by *Aspergillus* due to suture infection. Often lung transplant recipients receive universal antifungal prophylaxis with inhaled amphotericin.

The risk of CMV disease is higher than after kidney, heart or liver transplantation. CMV pneumonitis and bronchiolitis obliterans may develop. In these patients, EBV can cause mononucleosis or lymphoproliferative disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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