Role of viral infections in immunosuppressed patients

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Abstract Being a solid organ and hematopoietic stem cell transplant recipient as well as receiving chemotherapy for a malignant hematological disease clearly predispose the subject to a variety of viral infections, both common and opportunistic diseases. The patient may have encountered these infections from the community as well as from the donor organ (donor-derived infections) and/or from reactivation of an endogenous latent virus. Herpes viruses and especially the cytomegalovirus and Epstein-Barr virus are among the most common of the opportunistic viral pathogens affecting these patients, in addition to respiratory viruses. Treatment consists in antiviral drug therapies combined with the reduction in the degree of the induced immunosuppression. A review of the literature has been performed in order to update the epidemiology, pathogenesis, clinical manifestations and therapeutic approach of the viral infections in these immunocompromised patients.

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KEYWORDS
Viral infection; Cytomegalovirus; Respiratory viruses; Immunodepressed patients; Transplant

Papel de las infecciones víricas en pacientes inmunodeprimidos

Resumen Ser receptor de un trasplante de órgano sólido, así como recibir tratamiento quimio-terápico para una enfermedad hematológica maligna, predispone claramente a padecer infecciones virales tanto comunes como oportunistas, de origen tanto comunitario como procedentes del donante de órganos y/o de una reactivación de un virus latente endógeno. Herpes virus y más especialmente citomegalovirus y virus de Epstein-Barr son los que con más frecuencia afec- tan a estos enfermos, así como los virus respiratorios. El tratamiento consiste en la combinación de reducir la inmunodepresión inducida junto con tratamiento antiviral. Se ha realizado una revisión de la literatura pormenorizada y actualizada de la epidemiología, la patogenia, las manifestaciones clínicas y la aproximación terapéutica de las infecciones virales en estos enfer- mos.

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Patients with solid organ transplants and viral infections

Introduction

In the last two decades, solid organ transplantation (SOT) has become the treatment of choice for many diseases which in the past led to patient death due to the failure of one or more vital organs. In addition to developments in the different surgical and anesthetic techniques, there is no doubt that advances in immunosuppressor treatment have played a key role in allowing such improvements in therapy. Infections are the most frequent complications in transplant recipients, and are the main cause of death during the first year after transplantation. SOT recipients are particularly vulnerable to common or opportunistic viral infections. Such infections may derive from the donor organ (donor-derived infections) or may be community-acquired or correspond to the reactivation of latent endogenous viruses of the patient. Apart from the direct harmful effects of many of these viruses, mention must be made of the immune modulating and inflammatory actions of some of them, which can give rise to very important indirect effects such as acute or chronic graft rejection, or the favoring of other opportunistic infections.

The extensive herpesvirus family, and very particularly cytomegalovirus (CMV) and Epstein-Barr virus (EBV), are among the most frequent opportunistic viral pathogens causing infection in SOT patients. These viruses are closely followed in order of frequency and importance by herpes simplex virus (HSV), varicella-zoster virus (VZV) and type 6 human herpes virus (HHV-6), with the infectious syndromes typically produced by them. In the last two decades two new types of herpesvirus have been added: human herpes virus types 7 and type 8 (HHV-7, HHV-8), which cause proliferative or neoplastic diseases in these transplant patients. Other less common types of varied and characteristic processes produced by viral families such as papillomavirus (human papillomavirus [HPV]), polyomavirus (BK virus [BKV] and JC virus [JCV]) and erythrovirus B19 (previously referred to as parvovirus B19).

On the other hand, in certain types of SOT such as liver transplantation, hepatotropic viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are also important, and can condition transplant outcome.

In reference to the community-acquired viruses, practically any of them can cause infections in SOT patients, though in recent times special emphasis has been placed on respiratory viruses such as respiratory syncytial virus (RSV), influenza and parainfluenza viruses, metapneumovirus (MPV) and bocavirus, neurotrophic viruses such as lymphocytic choriomeningitis virus (LCMV), West Nile virus (WNV) and rabies virus, as well as the viruses that cause measles and mumps, coronavirus and rotavirus.

Modifying factors

Viral infections in SOT patients are conditioned by at least three groups of factors that modify their frequency and time and form of presentation:

• The transplanted organ, the surgical modality and technique used for transplantation, and the immune suppression protocol used.
• The relationship between the serological status of the donor and that of the recipient (D/R status).
• The prophylactic measures adopted to prevent the development of viral disease, universal prophylaxis, selective risk-adapted prophylaxis, prolonged prophylaxis, deferred prophylaxis or anticipatory therapy.

Infection risk periods

Viral infections, in the same way as infections caused by other microorganisms, follow a defined chronological pattern involving well defined periods (Fig. 1): in this interval the risk of infection is very high, and is fundamentally related to nosocomial bacteria and, to a lesser degree, fungi (Candida and Aspergillus) - with clinical manifestations similar to those found in other surgical patients. Viral infections are infrequent in this phase.

• The second period extends from the end of the postoperative interval to the sixth month. The risk of infection in this case is lower, and the microorganisms involved tend to be opportunistic organisms - including many of the aforementioned viruses.
• In the third period, starting from the sixth month after transplantation, the risk of infection decreases considerably, and the infections are usually produced by out-hospital microorganisms. During this period, a minority of patients in which the grafted organ does not evolve correctly may suffer infections that are more characteristic of the preceding two periods.

Clinical manifestations

Both the common and opportunistic viruses are able to produce a broad range of infectious syndromes with very different clinical behaviors in SOT recipients. The disorders may range from scantly expressive or oligosymptomatic clinical conditions, characterized only by fever and detectable viremia, to processes that are extremely serious because of serious structural and functional damage to the grafted organ (more susceptible to infection and greater damage) or to other target organs (due to special tropism shown by some viruses), or because of their disseminated and systemic nature. In this context, mention can be made of simple infection due to CMV with fever and cytomegaloviremia, but also of serious organ-specific disease such as enterocolitis (with hemorrhagic characteristics in some cases), pneumonia (including even a bilateral alveolointerstitial pattern with severe respiratory failure or adult respiratory distress syndrome [ARDS]), hepatitis, retinitis and encephalitis.

Very similar behavior can be shown by other viruses of the herpes family, such as HSV, VZV and HHV-6, causing more or less extensive and characteristic (vesicular or non-vesicular) exanthematic mucocutaneous disease, with the particularity of being able to spread to or affect other organs. Presentations of a particularly serious nature include...
hepatitis, pneumonitis, gastrointestinal forms (esophagitis and colitis), and especially the neuro-ophthalmological forms of meningoencephalitis, encephalomyelitis and retinitis. Fortunately, this viral family is susceptible to treatment with specific antiviral agents of established efficacy.\(^\text{19}\) In this context, EBV can cause various types of very distinct infectious syndromes (Table 1), though post-transplantation lymphoproliferative disease (PTLD) is of particular importance due to its clinical repercussions and exclusive management characteristics.\(^\text{20,21}\)

The polyomaviruses produce a broad range of relevant clinical conditions depending upon their tropism and invasiveness, giving rise to severe demyelination phenomena such as progressive multifocal leukoencephalopathy (PML) in the case of JCV and to a varied number of processes in the case of BKV,\(^\text{22,23}\) such as graft interstitial nephropathy (in renal transplants) - with the risk of transplanted organ loss, ureteral stenosis, hemorrhagic cystitis, meningoencephalitis or urothelial carcinoma (Table 2). Erythrovirus B19 shows a strong attraction for hematopoietic precursors, particularly of the red cell line, and can cause serious and refractory aplastic anemia and pancytopenia,\(^\text{24}\) as well as induce arthritis, rash and a risk of serious organ disease.

Both \textit{de novo} hepatitis and reactivations, reinfections or recurrences of the disease due to HBV and HCV can cause serious inconveniences for SOT patients and affect the prognosis and outcome of the transplant, particularly in the case of liver transplant patients. In contrast to HBV recurrence, which is effectively contained by specific immunoglobulins and antiviral agents, no effective prophylaxis against hepatitis C is available, and this disease is almost sure to prove recurrent. The post-transplant evolution depends on prevention of reinfection of the transplanted organ,\(^\text{25}\) limited by different host factors\(^\text{26}\) and by the toxicity of the antiviral drugs used against HCV - including pegylated interferons.\(^\text{27}\) A substantial proportion of HCV infected patients suffer terminal recurrent liver allograft disease, leading to diminished survival of the transplanted organ, an increased need for liver retransplantation, and ultimately a reduction in patient survival.\(^\text{28}\) These aspects have gained increased importance following the introduction early in the decade of liver transplantation procedures in patients coinfected with the human immunodeficiency virus (HIV) and HCV,\(^\text{29-31}\) since these individuals exhibit a faster cirrhosis progression rate that leads to an increased frequency of cirrhosis, terminal liver disease and hepatocellular carcinoma.

### Treatment

The treatment of viral infections in SOT patients with effective antiviral drugs must be complemented by a reduction in the grade and intensity of immune suppression.
The prevention of viral infections in SOT patients is of capital importance and can be achieved by implementing different measures such as vaccination programs and certain antiviral strategies, as has been accepted on a consensus basis in the case of CMV.

Viral infections in hematological patients

Introduction

Hematological patients present different types of immune disorders, depending on the hematological disease involved, its evolutive status, and the treatment provided. Such immune problems favor the development of serious infections that in turn increase patient morbidity-mortality.

In recent years, viral infections have gained importance in this group of patients, which in clinical practice can be classified as oncohematological patients, hematopoietic precursor cell transplant (HPCT) recipients, and blood product recipients. The epidemiology is changing, and the spectrum of severe viral infections is increasing among patients which until a few years ago did not usually suffer such infections. This largely has been a consequence of the use of new drugs with a marked immunosuppressor effect.

There are three types of immune deficiency: neutropenia, cellular immune deficiency and humoral immune deficiency. Each type of immune depression is associated with a certain type of infection; however, different types of immune deficiency tend to coexist in the case of hematological diseases.
Table 2  Emergent viruses in SOT: diagnostic methods, clinical presentations and treatment options

| Virus (seasonality)                  | Diagnosis                                      | Clinical manifestations                                                                 | Treatmenta                           |
|--------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------|
| Bocavirus (late autumn, winter)      | PCR                                            | Fever, rhinorhea, cough, diarrhea, disseminated infection                               | Unknown                              |
| Non-SARS CoV strains                | Culture, PCR                                    | Upper and lower respiratory tract infections                                            | −                                    |
| Erythrovirus B19                     | Serology, PCR, bone marrow biopsy               | Arthralgia/arthritis, anemia, pancytopenia, hepatitis, pneumonitis, myocarditis, glomerulonephritis | IG i.v.                              |
| HHV-6                                | PCR, culture in viral media, shell-vial culture, histopathology | Fever, hepatitis, pneumonitis, pancreatitis, meningoencephalitis, enteritis, gastritis, rash (short-lasting), pancytopenia, T cell dysfunction, thrombotic microangiopathy | Ganciclovir (variant A), foscarnet, cidofovir |
| Measles                              | Serology                                        | Fever, diarrhea, abdominal pain, dyspnea, headache, rash, hepatitis, prolonged PT, aseptic meningitis | Ribavirin (i.v.)?c                    |
| Metapneumovirus (end of winter)      | Culture, PCR                                    | Fever, rash, pneumonitis                                                               | −                                    |
| Parotiditis (mumps)                  | Serology, PCR                                   | Mumps, fever                                                                          | Podophlox or podophyllin tincture, imiquimod, interferon-alpha (local application) |
| Papillomavirus (HPV)                 | Histopathology, cytology, PCR, EM               | Anogenital papillomas and warts, cervical neoplasms                                   | Cidofovir,^c cytosine arabinoside?,^c leflunomide?^c |
| Polyomavirus (JCV, BKV)              | Histopathology, cytology, culture, PCR, EM      | CNS demyelination, PML, meningoencephalitis, severe nephritis with renal graft loss, ureteral stenosis, hemorrhagic cystitis, urothelial carcinoma, prostatic neoplasms | Anti-WNV IG i.v.?c                   |
| Rotavirus                            | Stool antigen detection tests, PCR, EM          | Diarrhea, gastrointestinal bleeding                                                    | −                                    |
| West Nile virus (end of summer, autumn) | Serology, CSF capture IgM antibodies, PCR       | Fever, malaise, headache, myalgia, meningitis, encephalitis, pseudo-poliovilletic syndrome, hyporeflexia | −                                    |

BKV: BK virus; CoV: coronavirus; i.v.: intravenous route; IF: immunofluorescence; anti-WNV IG i.v.: intravenous specific immunoglobulins against West Nile virus; IG i.v.: intravenous immunoglobulins; PML: progressive multifocal leukoencephalopathy; EM: electron microscopy; PCR: polymerase chain reaction; SARS: severe acute respiratory syndrome; CNS: central nervous system; PT: prothrombin time; p.o.: oral route; LCMV: lymphocytic choriomeningitis virus; HHV-6: type 6 human herpes virus; JCV: JC virus; HPV: human papillomavirus.

aWhere possible, treatment should include a reduction in the intensity of immunosuppressor treatment.

bThe PCR results are to be interpreted with caution when the possibility of latent infection exists.

cTherapies that might be used, though their efficacy has not been sufficiently established.

dMay have a certain in vitro activity, though the in vivo usefulness is not known.
Neutropenia predominates in patients with acute leukemia, marrow aplasia or evolved myelodysplastic syndromes, and in patients subjected to intensive chemotherapy. In these situations the infections are predominantly caused by grampositive and gramnegative bacteria, fungi and viruses (herpes, RSV, influenza, parainfluenza).

Cellular immune deficiency in turn appears in patients with Hodgkin’s lymphoma and other advanced lymphoproliferative syndromes, in treatments with glucocorticoids, purine analogs and treatments with monoclonal antibodies. In these situations it is common to find infections caused by intracellular bacteria, viruses (CMV, HSV, V2V, JCV, HHV-6, RSV), fungi and parasites.

Lastly, humoral immune deficiency predominates in patients with multiple myeloma, Waldenström’s macroglobulinemia, chronic lymphatic leukemia (CLL) and splenectomized subjects. Infections are less frequent than in the previous groups and are fundamentally caused by encapsulated bacteria.

HPCT is a treatment option in hematological diseases, mainly in malignant blood disorders. Infection is an important complication, due to the summative immune depression caused by the background neoplastic disease itself, the conditioning regimen administered for transplantation, and the treatment of rejection and of graft-versus-host disease (GVHD). Other infection risk factors are the consideration of whether the donor is a relative or not, the patient viral serology condition prior to transplantation, and the time of development of the infection after transplantation.

**Risk periods**

There are three predictable immune deficiency risk periods in HPCT:

- **Immediate post-transplant period:** This starts with conditioning treatment and persists up to 30 days after transplantation. This period is characterized by intense neutropenia and lymphocytopenia. Regarding viral infections in this phase, the most common condition is the reactivation of HSV in previously seropositive patients.

- **Early post-grafting period:** This starts with neutrophil recovery and persists up to day 100, when functional recovery of the B and T cells occurs. However, the presence of GVHD and its treatment may delay such immune recovery. CMV is the most important infectious agent in this phase. Other viral infections of note in this phase are those produced by RSV, influenza and parainfluenza virus, rhinoviruses, gastroenteritis due to rotavirus and Coxsackie virus, or reactivations of adenoviruses and HHV-6.

- **Late post-grafting period:** This extends from day 100 to the recovery of normal immunity, 18-36 months after HPCT, provided the patient is not subjected to immune suppression and remains free of GVHD. In this period there may be reactivation of V2V, and infection due to CMV (particularly in seropositive patients with chronic GVHD).

**Principal agents**

*Herpes simplex virus:* The most frequent clinical manifestation is gingivostomatitis, though in some cases the disease can spread to the esophagus, larynx or skin of the perioral and perianal regions. It is sometimes difficult to distinguish between mucositis caused by HSV and that caused by the chemotherapy itself; as a result, empirical antiviral therapy is usually indicated. The reactivation of HSV can be reduced from 80% to less than 5% in seropositive recipients during the first month after transplant by prescribing aciclovir or valaciclovir from the time of conditioning and until recovery from mucositis (see treatment and prophylaxis in Table 3). 1,3,4,19

*Varicella zoster virus:* This manifests as a primary infection (5%) or as reactivation (95%) in 40% of the patients at some time during the first year after transplant, in patients with important cellular immune deficiency (Hodgkin’s lymphoma), and in patients in which the condition was previously not common (CLL) and who had received treatment with new immunosuppressor drugs (fludarabine, rituximab, alemtuzumab). In addition to the typical cutaneous forms of presentation, hemorrhagic pneumonia, hepatitis, central nervous system involvement, thrombocytopenia and retinal necrosis may be observed. Occasionally in patients with HPCT, visceral involvement can occur without preceding skin lesions. GVHD is a potent predictor of dissemination. Mortality increases in the presence of lung involvement. The treatment is summarized in Table 3. 3,8,19

*Cytomegalovirus:* CMV infection is an important complication in patients subjected to HPCT, for although the incidence of CMV disease has decreased in recent years thanks to the prevention strategies adopted, CMV seropositivity is considered an independent risk factor for GVHD and is associated with poorer survival, increased mortality due to bacteremia and fungal infections, and with transplant-related mortality. 4 The manifestations of CMV infection of the target organs are pneumonia, enterocolitis and (more rarely) retinitis. CMV pneumonia is the most frequent and serious manifestation, for even with treatment the mortality rate is 30-50%. This disorder is infrequent prior to graft consolidation, however. On the other hand, CMV pneumonia is being seen to behave as an emerging infection in adult leukemia patients treated with immunosuppressor drugs. 41 HPCT recipients can be classified into different CMV disease risk groups. High risk is assumed for allogenic transplants if there is T cell depletion of the precursor cell source, if the donor is not a relative, in the absence of identical histocompatibility antigen (HLA), the use of high-dose corticosteroids, treatment with alemtuzumab and purine analogs, and autologous transplants with CD34+ selection, treated with purine analogs and high-dose corticosteroids (Table 3). The diagnostic techniques of choice for early detection of the infection are antigenemia and PCR. In relation to the diagnosis, it important to apply consensus-based criteria of infection and disease. 42 The regimens relating to prophylaxis, anticipatory treatment and guided treatment are explained in Table 3.

Community-acquired respiratory tract viruses: The most frequent in patients subjected to HPCT and in leukemia patients subjected to chemotherapy are paramyxoviruses (RSV, parainfluenza virus, 1,3 metapneumovirus), orthomyxoviruses (influenza A and B), rhinovirus, coronavirus NL63 and HKU1, adenoviruses and bocavirus, among others. Respiratory viral infections tend to manifest in relation to seasonal outbreaks and are acquired through contact with
other infected individuals. If pneumonia develops, the associated mortality rate is high—particularly in the case of RSV and parainfluenza virus. There are no treatments of established efficacy for such infections, though inhalatory ribavirin is recommended in the case of RSV pneumonia, and neuraminidase inhibitors (oseltamivir, zanamivir) are advised in the case of influenza virus. No effective chemoprophylactic measures are available for these infections in oncohematological patients; it is therefore essential to prevent these patients from becoming exposed to these viruses, including nosocomial transmission.

**Adenoviruses:** Infection as a consequence of viral reactivation can occur in approximately 10% of all allogenic HPCT recipients, and in a smaller proportion of autologous HPCT recipients. The most frequent manifestation is the hemorrhagic cystitis, though systemic pulmonary, hepatic, gastrointestinal and renal infection can also develop. GVHD is an adenovirus infection risk factor following HPCT. There is no effective treatment for this infection.

**Other viruses:** Erythrovirus B19 in patients with chronic hemolytic anemia produces red-cell aplastic episodes. In HPCT patients it is an infrequent cause of anemia. The polyomaviruses (JC virus and BK virus) can give rise to progressive multifocal leukoencephalopathy (PML) and hemorrhagic cystitis, respectively. Most cases of EBV reactivation are subclinical and do not require treatment, though in other cases pleomorphic T lymphoma (PTL) of high mortality may result. HHV-6 in HPCT can give rise to situations of myelo suppression, skin rash, meningoencephalitis and GVHD exacerbation. HHV-8 in turn has been related to bone marrow hypoplasia, Kaposi’s sarcoma, multicentric Castleman’s disease, and cavity B cell lymphoma.

**Viral infections and new immunosuppressor drugs**

Treatment with fludarabine (a purine analog) and alemtuzumab (anti-CD52 IgG1 kappa humanized monoclonal

| Prevenion | Treatment |
|-----------|-----------|
| HSV       | HSV seronegative patients: no prophylaxis HSV seropositive patients subjected to allogenic HPCT (also recommended in patients subjected to autologous HPCT in which severe mucositis is expected during conditioning) • Aciclovir i.v. 250 mg/m²/12 h or 5 mg/kg/12 h • If tolerated: oral aciclovir 400 mg/8-12 h Valaciclovir 500 mg/24 h | Stomatitis: • Aciclovir i.v. 250 mg/m²/8 h or 5 mg/kg/8 h |
| VZV       | Vaccine: contraindicated, except in children with ALL in remission Chemoprophylaxis: consensus is lacking After risk exposure: • Specific gammaglobulin (under 96 h) • Alternative: aciclovir (started 7-9 days after exposure) 800 mg/6 h during 7 days | Non-complicated, localized infection: • Oral aciclovir 800 mg 5 times a day • Valaciclovir 1000 mg/8 h • Foscarnet 500 mg/8 h |
| CMV       | Low risk: • Autologous/syngeneic: without specific measures • Allogenic donor and CMV (-) recipient: CMV (-) or filtered hemotherapy Intermediate/high risk: Aciclovir i.v. 10 mg/kg/8 h; p.o. 800 mg 5 times a day (when tolerated) • Valaciclovir p.o. 1000 mg 4 times a day • Ganciclovir i.v. 5 mg/kg/12 h for 5 days, followed by 5 mg/kg/day | Anticipatory or early treatment: Ganciclovir i.v., induction (I): 5 mg/kg/12 h; maintenance (M): 6 mg/kg/24 h Foscarnet i.v. I: 60 mg/kg x 2/24 h; M: 90 mg/kg/24 h |
| CMV       | • Cidofovir i.v. I: 3 mg/kg once a week x 2 doses; M: 3-5 mg/kg every 2 weeks Valganciclovir p.o. I: 900 mg/12 h; M: 900 mg/24 h | Complicated, disseminated infection: • Aciclovir i.v. 500 mg/m²/8 h or 10 mg/kg/8 h Treatment of disease: • Pneumonia: ganciclovir 5 mg/kg/12 h x 14-21 days, followed by 5 mg/kg/24 h x 3-4 weeks + immunoglobulins i.v. • Gastrointestinal infection: ganciclovir 5 mg/kg/12 h x 14-21 days followed by 5 mg/kg/24 h x 3-4 weeks |
| CMV       | • Aciclovir i.v. 500 mg/m²/8 h or 10 mg/kg/8 h | Pneumonia: ganciclovir 5 mg/kg/12 h x 14-21 days, followed by 5 mg/kg/24 h x 3-4 weeks + immunoglobulins i.v. |
| CMV       | CMV (-) Foscarnet i.v. I: 60 mg/kg x 2/24 h; M: 90 mg/kg/24 h | Pneumonia: ganciclovir 5 mg/kg/12 h x 14-21 days, followed by 5 mg/kg/24 h x 3-4 weeks + immunoglobulins i.v. |
| CMV       | Foscarnet i.v. I: 60 mg/kg x 2/24 h; M: 90 mg/kg/24 h | Pneumonia: ganciclovir 5 mg/kg/12 h x 14-21 days, followed by 5 mg/kg/24 h x 3-4 weeks + immunoglobulins i.v. |
| CMV       | | Pneumonia: ganciclovir 5 mg/kg/12 h x 14-21 days, followed by 5 mg/kg/24 h x 3-4 weeks + immunoglobulins i.v. |
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| CMV       | | Pneumonia: ganciclovir 5 mg/kg/12 h x 14-21 days, followed by 5 mg/kg/24 h x 3-4 weeks + immunoglobulins i.v. |
antibody) is associated with an increased frequency of infections due to HSV and VZV, and to infection and disease caused by CMV. Rituximab (a chimerical monoclonal antibody targeted to the CD20 receptor) has been associated with unusual infections such as PML, retinitis, and CMV pneumonitis.

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