

## Practical approach by main clinical syndromes

Jose Tiago Silva  
Francisco López-Medrano  
Jose Maria Aguado

# Highlights in solid transplant infectious diseases 2015-2017

Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Instituto de Investigación Hospital "12 de Octubre" (i+12), School of Medicine, Universidad Complutense. Madrid, Spain.

### ABSTRACT

Solid organ transplant recipients have an increased risk of developing infections due to the lifelong treatment with immunosuppressive drugs. Herein we review recent (2015-2017) and relevant published advances in the field of bacterial, viral and fungal-infections in this population. We also address the most up-to-date immunological assays that can predict the risk of infection. Finally, we review current guidelines and how they improve the usual clinical care.

**Key words:** Solid organ transplant; infectious diseases; immunosuppression

### Lo más destacado en infección en trasplante de órgano sólido 2015-2017

### RESUMEN

Los receptores de un trasplante de órgano sólido tienen un mayor riesgo de desarrollar infecciones secundario a la inmunosupresión. En este artículo, revisamos los avances más recientes (2015-2017) y significativos en el campo de las infecciones bacterianas, virales y fúngicas en esta población. También revisamos los estudios inmunológicos que midiendo la respuesta inmune pueden predecir el riesgo de desarrollar una infección. Por último, revisamos las guías clínicas más recientes y cómo pueden mejorar la atención prestada a estos pacientes.

**Palabras clave:** Trasplante de órgano sólido; enfermedades infecciosas; inmunosupresión

Correspondence:  
Francisco López Medrano  
Unit of Infectious Diseases, Hospital Universitario "12 de Octubre". Centro de Actividades Ambulatorias, 2ª planta, bloque D. Avda. de Córdoba, s/n. Postal Code 28041. Madrid, Spain.  
Phone: +34 913908000. Fax: +34 914695775.  
E-mail: flmedrano@yahoo.es

### INTRODUCTION

Several important advances have been made in the field of solid organ transplant infection in recent years. These advances have given origin to better prophylactic, empirical and directed treatments and a more appropriate and effective follow-up. In this article, we shall review the most significant developments in the field of viral, bacterial and fungal-related infection and the changes they have brought to the daily clinical care. We will also review the latest in immunity assays and their capability in predicting the risk of infection. We also discuss the novelty aspects of recently published guidelines.

### WHAT IS NEW IN THE FIELD OF VIRAL INFECTION?

Ganciclovir-resistant (GCV-R) cytomegalovirus (CMV) has emerged as an important opportunistic pathogen after transplantation. Nevertheless, most of the published studies that have focused on this problem had important limitations, such as small number of patients and limited information on clinical outcomes. By designing a retrospective, case-control study which matched 37 genotypically confirmed GCV-R CMV cases to 109 GCV-S CMV controls, Fisher et al. were able to determine the risk factors and outcomes directly associated to GCV-R CMV infection [1]. The authors observed that longer duration of antiviral treatment (153 days [121-208] vs 91 days [41-108],  $P < 0.001$ ) and a higher viral load (61,250 IU/mL [30,000-142,500] vs 8,125 IU/mL [1,913-37,500],  $P < 0.001$ ) were important predisposing factors for developing resistance to GCV. GCV-R CMV infection was also associated to a significantly worse one-year survival rate when compared to GCV-S CMV infection.

Relapse of CMV infection following treatment can occur in 20-30% of transplant recipients. For this reason, following a successful treatment, most clinicians tend to use a long-term secondary prophylactic strategy. Nevertheless, no randomized trials or observational studies have demonstrated the effec-

tiveness of secondary prophylaxis. Gardiner et al. designed a retrospective cohort study, which compared the relapse time of CMV infection between recipients who received secondary prophylaxis and those who did not [2]. All of the 120 patients who received secondary prophylaxis and all of the 50 patients in the control group had been previously treated for an episode of CMV disease. The authors observed that secondary prophylaxis was associated with a reduced risk of early relapse, but that there was limited residual protective effect after stopping prophylaxis. They concluded that secondary prophylaxis could be useful in delaying an early relapse of CMV infection, especially in high-risk patients [2].

Although lung transplant recipients are constantly exposed to respiratory viruses, the epidemiology data of respiratory virus infections in this population and their relationship with chronic lung allograft dysfunction, acute rejection and opportunistic infections are not well known. A recent prospective study, performed from 2009 to 2014, enrolled 98 lung transplant recipients. A total number of 1094 nasopharyngeal swabs were collected from these patients and analyzed by multiplex polymerase chain reaction [3]. These included asymptomatic patients, patients diagnosed with upper or lower respiratory tract infection and patients with biopsy-proven acute rejection. The mean follow-up period was 3.4 years. The authors described that the incidence of respiratory virus infections in lung transplant recipients was very high (a 23.6% positivity rate) and associated with direct effects (tracheobronchitis and pneumonia) and indirect effects (immediate allograft dysfunction, *Pseudomonas aeruginosa* colonization and infection, and CMV replication and disease) [3].

Complications after influenza infection in solid organ transplant recipients can be severe. It is recommended that all recipients receive the annual inactivated trivalent influenza vaccine. Although this strategy is the most effective approach in reducing the burden of influenza disease, it is well known that the rates of seroprotection in this group of patients is generally lower than of the general population. TRANSGRIPE 1-2 is a phase 3, randomized, controlled, multicenter, open-label clinical trial. It hypothesized that the rate of seroprotection could be increased by administering a second dose of the influenza vaccine 5 weeks after the first dose in solid organ transplant recipients [4]. Approximately 500 liver, kidney, heart and lung transplant recipients were randomly assigned (1:1 ratio) to receive one or two doses of influenza vaccine. The authors observed that the rate of seroprotection was higher in the two doses group for all the influenza virus analyzed: 54% vs 43.2% (OR 1.54 [95% CI, 1.05–2.27];  $P = 0.026$ ) for influenza A(H1N1), 56.9% vs 45.5% (OR 1.58 [95% CI, 1.08–2.31];  $P = 0.020$ ) for influenza A(H3N2) and 83.4% vs 71.8% (OR 1.97 [95% CI, 1.23–3.16];  $P = 0.004$ ) for influenza B [4]. There was no difference in the rate of adverse events between both groups. The authors concluded that the administration of two doses of the influenza vaccine was safe and associated with an improved immunological effectiveness (in all the cases the vaccine was administered after the first month of transplantation) [4].

The THINKER study explored deliberated hepatitis C virus (HCV) transmission from donor to receptor in kidney transplantation in the era of direct acting antivirals. The investigators sought to determine if it was safe to transplant kidney grafts from HCV genotype 1-viremic donors to HCV-negative recipients, who were treated for 12 weeks with elbasvir-grazoprevir as soon as HCV viral load became detectable after transplantation [5]. The entire group of 10 kidney transplant recipients developed a positive HCV viral load on day 3 after transplantation and all of them achieved a sustained virologic response 12 weeks after the end of treatment for HCV, with no deleterious effect on the graft function [5].

## WHAT'S NEW IN THE FIELD OF BACTERIAL INFECTION?

Should asymptomatic bacteriuria (AB) be systematically treated in kidney transplant recipients? That is the question that the study group of the University Hospital 12 de Octubre (Madrid, Spain) sought to answer. For that, the group prospectively randomized 112 kidney transplant recipients who had undergone transplantation from January 2011 to December 2013 in two groups: the treatment group, in which the episodes of AB were systematically treated, and the control group, in which no treatment was prescribed [6]. The authors observed that only 3.6% of AB episodes had followed by symptomatic urinary tract infection (UTI) caused by the same microorganism, that one-third of pyelonephritis had no preceding AB episode and that 32.7% of AB episodes had spontaneously cleared without antibiotic treatment. The authors concluded that AB systematic screening and treatment (beyond the second month of transplantation and in patients without ureteral stents or urinary catheters) has no apparent benefit [6].

## WHAT'S NEW IN THE FIELD OF FUNGAL INFECTION?

Lung transplant recipients have the highest risk for developing invasive pulmonary aspergillosis (IPA) when compared to other transplant groups, such as liver or kidney transplant recipients. The risk factors, prognosis, prophylaxis and treatment of API in lung transplant recipients are well known and optimized. The incidence of IPA in kidney transplantation is much lower than in lung transplantation but the former is performed much more frequently than the latter worldwide. That is why, in absolute terms, there are much more IPA every year in kidney transplantation than in any other type of solid organ transplantation. Notwithstanding, the current knowledge of the risk factors for developing IPA in the first six months of transplantation and the determinants of mortality was limited to case reports or small case series. López-Medrano et al. developed a multinational retrospective cohort study that included 29 hospitals located in 6 different European countries and 4 different American countries [7,8]. The centers included cases of probable or proven IPA cases diagnosed in kidney transplant recipients from January 1, 2000 to December

31, 2013. To determine the risk factors for developing IPA, a control group (1:1 ratio), consisting of the patients who had undergone transplantation immediately before or after the index cases at each center was created; the control group was matched by institution and date of transplantation and had to have survived at least until the diagnosis of IPA in the corresponding index case. A total number of 112 recipients were enrolled (25% proven IPA and 75% probable IPA). The authors concluded that pretransplant Chronic Obstructive Pulmonary Disease (COPD), impaired graft function (defined by the necessity of hemodialysis after transplantation) and the occurrence of bacteremia were risk factors for developing IPA [7]. The diagnosis of IPA within the first 6 months after transplantation (hazard ratio [HR]: 2.29;  $P = 0.027$ ) and bilateral involvement at diagnosis (HR: 3.00;  $P = 0.017$ ) were independent predictors for 6-week all-cause mortality, whereas the initial use of a voriconazole-based therapy regimen showed a protective effect (HR: 0.34;  $P = 0.007$ ) [8].

## WHAT'S THE LATEST IN IMMUNITY ASSAYS?

Transplant recipients have a higher risk of developing infections due the use of lifelong immunosuppressive drugs. Both acute and chronic allograft rejection episodes increase this risk as its treatment is based on a substantial increase of the doses of the administered immunosuppressive drugs. In order to reduce the risk of infection, standard prophylactic treatments for CMV, *Pneumocystis jirovecii* or *Toxoplasma gondii* are prescribed. Nevertheless, in most cases, the capability of the immune system to build a response against these microorganisms is not measured. Mian et al. designed a prospective observational cohort study using a new global cell-mediated immunity (CMI) assay (QuantiFERON Monitor® [QFM®], Qiagen), which measures plasma interferon-gamma (IFN- $\gamma$ ) levels after stimulation of whole blood with a combination of antigens that provokes both the innate and adaptive of the immune system [9]; IFN- $\gamma$  levels were measured at month 1, 3, and 6 after transplantation [9]. The authors hypothesized that a lower immune response would be associated with an increased risk of infection, while a normal/high response would be protective. Of the 151 consecutive solid organ transplant recipients who were enrolled in the study, 137 had a CMI measurement at least at one point during follow-up. CMI increased during follow-up; the difference of IFN- $\gamma$  levels between recipients appeared to be related with the dose of the administered immunosuppressive drugs, particularly prednisone (median, 15 mg [IQR, 15-20] vs 5 mg [IQR, 5-8];  $P < 0.0001$ ) and mycophenolate (median, 720 mg [IQR, 720-720] vs 530 mg [IQR, 360-720];  $P < 0.0001$ ) [9]. There were no significant differences of the IFN- $\gamma$  levels between patients treated for rejection and those that had not been diagnosed with rejection. Globally, patients who had developed at least one episode of infection during follow-up had significantly lower IFN- $\gamma$  levels at month 1 ( $P = 0.040$ ), month 3 ( $P = 0.050$ ) and month 6 ( $P = 0.006$ ) [9]. Patients with at least one episode of opportunistic infection also had lower IFN- $\gamma$  levels in month 3 ( $P = 0.024$ ) and month 6 ( $P = 0.014$ ) after transplantation. The authors concluded that CMI

testing could be useful in predicting the risk of infections after transplantation, although further studies would be required to determine the optimal IFN- $\gamma$  level cutoff [9].

## WHAT'S NEW IN RECENT GUIDELINES?

Guidelines are extremely useful for daily clinical care. They help clinicians to optimize their therapy and guide towards the most useful complementary tests depending on the clinical context. Three interesting guidelines have been published recently. Torre-Cisneros J et al. have published an expert consensus document concerning the management of CMV in this type of patients, which includes prophylactic and directed treatment, therapeutic alternatives for ganciclovir-resistant CMV infections and future strategies such as immunological therapy and new drugs [10]. Aguado JM et al. have published several recommendations concerning the management of infections by extended-spectrum  $\beta$ -lactamases (ESBL)-producing Gram-negative bacilli, carbapenemase-producing Enterobacteriaceae, carbapenemase-producing *Pseudomonas aeruginosa* and carbapenemase-producing *Acinetobacter baumannii* in solid organ transplant recipients [11]. Antibiotic alternatives and possible therapeutic schemes are detailed according to microorganism and mechanism of resistance. Finally, Clemente W et al. have published their recommendations on the management of endemic or geographically restricted diseases in solid organ transplant recipients [12]. The supplement, which counted with the expertise of clinicians from 13 different countries representing four continents, includes a carefully written review of relevant diseases such as tuberculosis, Chagas disease, leishmaniasis, malaria, strongyloidiasis, schistosomiasis, travelers' diarrhea, arboviruses (Chikungunya, Dengue, Yellow Fever and Zika), endemic fungal infections (histoplasmosis, paracoccidioidomycosis and sporotrichosis, coccidioidomycosis and *Cryptococcus gattii* infections) and viral hepatitis. The authors have also reviewed the most effective vaccines to mitigate the risk of vaccine-preventable diseases among this immunosuppressed population [12].

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