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Prevalence of Donor-Associated Infections in Lung Transplant Recipients

Authors: Balcázar Torres Jonathan, Ossés Juan Manuel, Calderón Juan, Vicente Luis, Nazzo Viviana, Carrasco Gladys, Ahumada Rosalía, Ibáñez Teresa, Favaloro Roberto, Candiotti Mariano, Bertolotti Alejandro, Cáneva Jorge Osvaldo

Institution: Hospital Universitario Fundación Favaloro, CABA, Argentina

Abstract

The infectious complication is the most common condition after a transplantation. There is a limited description regarding the prevalence of donor-associated infections (DAIs) in lung transplant (LTx) recipients. There are reports of DAIs in LTx recipients of 7.6%, with documented prophylactic failure of 5.6%.

Objective: to estimate the frequency of donor-associated infections after lung transplantation and their outcome in terms of overall survival (OS).

Methodology: an observational, descriptive study, carried out in a transplant center in Argentina between January 2018 and June 2020. The study included all the patients who underwent a transplantation within such period and those with defined/proven DAIs.

Results: during the aforementioned period, 65 LTx were performed in 64 individuals (one patient underwent transplantation and subsequent retransplantation in the same study period). The median age was 39 (12-72) years. Cystic fibrosis was the main reason for transplantation (26.2%) In 61/65 cases (94%), germs were isolated from biological samples collected from the donor: 78.6% in the preservation liquid, 73.7% in donor secretions, 21.3% surgical samples, and 4.9% blood cultures. Donor-associated infections were identified in 2/61 cases (prevalence of 3.1%; 95% CI: 0.4-10.7%), with a median posttransplant OS of 12 months, and an OS of 98.4% (95% CI: 91.7-99.9%).

Conclusion: the prevalence of DAIs in LTx recipients in the present series was 3.1%: higher than the figures documented for solid organ transplants in general (< 1%), but lower than the numbers found in the few published reports (7.6%).

Key words: Infection; Donor; Transplant; Lung

Introduction

Lung transplantation (LTx) has become an accepted treatment option for end-stage pulmonary parenchymal and vascular diseases. The donor's pretransplant screening is very important and should be conducted rigorously in order to minimize as much as possible the risk of transmission of certain infectious processes.

This study has the objective of estimating the frequency of donor-associated infections after LTx and their outcome in terms of overall survival. Complications occur frequently and may lead to medium or long-term graft dysfunction and a decrease in survival. According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), LTx 1-, 2- and 5-year survival rates are 80%, 65%, and 53%, respectively[1].

Donor-derived disease transmissions are defined as any disease present in the organ donor that is trans-

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Correspondence: Jonathan Balcázar Torres: jtorres@ffavaloro.org; drjmbt2012@gmail.com

mitted to at least one of the recipients[1]. Bacteria or fungi can be transferred to the donor graft through contamination during recovery, preservation or manipulation, or during the transplantation. Infectious complications are a common cause of morbidity and mortality, and the most important cause of death during the first year. More than two thirds of those conditions affect the respiratory tract[1]. The prognosis for LTx recipients has considerably improved in recent years, thanks to the thorough selection of donors and recipients, and better surgical techniques, postoperative care and graft preservation methods.

This work addresses specific aspects of DAIs, which are one of the most important problems that need to be handled during the first days after LTx. So, more studies are necessary in order to answer questions about DAIs in LTx recipients.

Materials and Methods

Study Design

This is an observational, descriptive, prevalence study. It was designed in accordance with the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) declaration. It was carried out in patients who underwent a LTx at the Hospital Universitario Fundación Favaloro (HUFF) between January 2018 and June 2020.

Population and sample

Inclusion criteria. Patients who underwent a LTx basing on the ISHLT standards, according to the prioritization criteria for the allocation of organs for transplant of the Unique Central National Institute Coordinator of Ablation and Implant (INCUCAI, for its acronym in Spanish), regardless of the age group, condition or type.

Transmission events reported in this review refer to proven/defined cases in compliance with the definitions of imputability for donor origin of disease transmission (according to USA and Europe literature)[2]. A DAI is considered as proven (according to the American criteria) whenever there is clear evidence of the same infectious disease in the donor and at least one of the recipients, and all the following conditions must be fulfilled: suspected transmission event, laboratory evidence of suspected organism (or malignancy) in a recipient, laboratory evidence of the same organism (or malignancy) in other recipients (if there are several recipients), laboratory evidence of the same organism or malignancy in the donor, and if there is pretransplant laboratory evidence, it shall indicate that the same recipient tested negative for this organism before the transplant. A DAI is considered as defined or true (according to the European criteria) when there is conclusive evidence beyond reasonable doubt for attributing the disease to the process or the transplanted organ[2].

Exclusion criteria. This review didn't take into account cases in which subsequent clinical follow-up wasn't possible.

Data collection. Data were collected in an encrypted, online Microsoft Excel 365 electronic spreadsheet.

Statistical analysis

Technical considerations. A p-value < 0.05 was considered statistically significant. The statistical analysis was conducted with the R v.3.6.3 program (R Foundation for Statistical Computing; Vienna, Austria).

Sample size calculation. Considering a 95% confidence interval (CI), a 5% margin of error, and a general DAI rate between transplants of 1% (Theodoropoulos N & Ison M, Transplant Infections, 2016), we estimated a required sample of 16 cases.

Descriptive statistics. Numeric variables were described as mean (standard deviation) or median (interquartile range, IQR), according to their statistical distribution (Kolmogórov-Smirnov test). Descriptive variables were described in frequencies (percentages), with their respective confidence interval (95% CI), if applicable.

Ethical considerations

The research protocol was approved by the HUFF Ethics Committee. All the patients signed the corresponding informed consent for attendance purposes. Data custody was guaranteed at all times pursuant to Personal Data Protection Law No. 25.326 (Ministry of Justice and Human Rights, Argentine Republic). This research was conducted in accordance with the Nuremberg Code of 1947, and the Declaration of Helsinki of 1964 and subsequent amendments (last version, 2013).

Results

A total of 65 LTx were performed in 64 individuals in our hospital between January 2018 and June 2020 (one patient underwent a transplantation and subsequent retransplantation within the same study period). All the individuals were followed up until the end of the study period. The median age was 39 years (12-72); 29/64 were females (45.3%). **Table 1** summarizes the sociodemographic characteristics of the patients included in the study.

Cystic fibrosis (CF) was the main reason for performing a LTx (17/65; 26.2%), followed by chronic obstructive pulmonary disease (COPD) (12/65; 18.5%), idiopathic pulmonary fibrosis (IPF) (11/65; 16.9%) and idiopathic pulmonary arterial hypertension (IPAH) (11/65; 16.9%). 30/65 cases (46.2%) met the criteria for an emergency transplant. 53/65 cases (81.5%) underwent a double-lung transplantation. 5/65 cases (7.7%) underwent a retransplantation, taking into account the fact that within this study period there was one case in which the patient underwent a transplantation and a subsequent retransplantation at the end of the study. (**Table 2**).

From all the LTx that were carried out (n=65), at least one germ was isolated in 61/65 (94%) biological samples collected from the donor (**Table 3**). The main germs isolated from these samples were methicillin-sensitive Staphylococcus aureus (MSSA) (28/61; 45.9%), followed by Haemophilus influenzae (HE) (7/61; 11.4%), coagulase-negative staphylococcus (CoNS) (5/61; 8.1%), and Streptococcus viridans (4/61; 6.5%); other germs (40/61; 65.5%) (**Figure 1 and Table 4**).

Donor-associated infections were identified in 2/61 (3%) cases which are detailed in **Table 5**. Both cases received targeted treatment according to the sensitivity of the rescue medication, and a frequency of 3.1% (95% CI 0.4-10.7%) and a 12-month posttransplant median overall survival (interquartile range, IQR 6-23) were identified in the total number of transplants. One patient died from a DAI, after devel-

TABLE 1. Sociodemographic characteristics of the study population

	(n = 64)
Age (years). median (range)	39 (12-72)
Minor (<18 years)	6 (9.4)
Young adult (18-39 years)	27 (42.2)
Adult (40-64 years)	26 (40.6)
Older adult (≥ 65 years)	5 (7.8)
Gender (female). n (%)	29 (45.3)
Nationality (Argentinian). n (%)	49 (76.6)
Insurance type. n (%)	
Social Security of State Institutionsa	12 (18.8)
Private Health Insurance	21 (32.8)
Prepaid Medical Care	16 (25.0)
International Health Insurance	15 (23.4)

Integrated Medical Services Program (PAMI, for its acronym in Spanish), local government entities, law enforcement authorities, Armed Forces

TABLE 2. Clinical conditions associated with lung transplantation

	(n = 65)
Reason for transplantation, n (%)	
CF	17 (26.2)
COPD	12 (18.5)
IPF	11 (16.9)
IPAH	11 (16.9)
Fibrotic HP	5 (7.7)
BCH	4 (6.2)
Bronchiolitis obliterans secondary to GvHD	2 (3.1)
Pulmonary fibrosis secondary to collagenopathy	1 (1.5)
LAM	1 (1.5)
CEP	1 (1.5)
Transplant prioritizationa, n (%)	
Emergency	30 (46.2)
Emergency type A	7 (10.8)
Emergency type B	15 (23.1)
Elective	13 (20.0)
Type of transplanta, n (%)	
Single-lung	12 (18.5)
Double-lung	53 (81.5)
Retransplantation, n (%)	5 (7.7)

[a] According to the prioritization criteria described by the Unique Central National Institute Coordinator of Ablation and Implant (INCUCAI, according to its acronym in Spanish).
CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; IPAH: idiopathic pulmonary arterial hypertension; HP: hypersensitivity pneumonitis; BCH: bronchiectasis; GvHD: graft-versus-host disease; LAM: lymphangioleiomyomatosis; CEP: chronic eosinophilic pneumonia.

TABLE 3. Biological samples extracted from the donor from which the different germs were isolated

Preservation liquid	(n = 61)
Preservation liquid	48 (78.6)
Secretions	45 (73.7)
Surgical samples	13 (21.3)
Peripheral hemocultures	3 (4.9)

oping septic shock secondary to a skin and soft tissue infection of the surgical wound and pneumonia with isolation of candida sp., sensitive to amphotericin B, vorinocazole, caspofungin and anidulafungin. The patient did not respond to treatment with azoles with susceptibility testing and adequate plasma concentrations of the drugs in use. (**Figure 2**). It is surprising that the two cases that showed donor-associated infection met the prioritization criteria for an emergency transplant.

Discussion

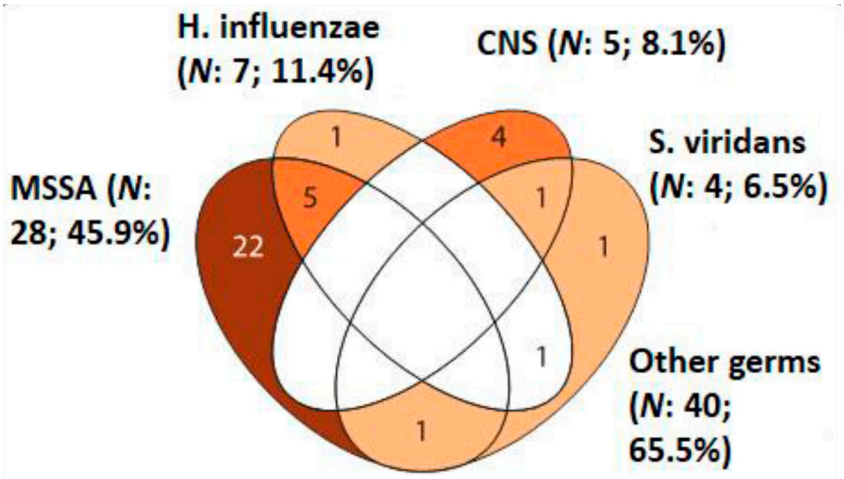

Figure 1. Intertwining of the distribution of germs most frequently isolated in the biological samples obtained from the donors

TABLE 4. Isolated germs

	(n = 64)	
Methicillin-sensitive Staphylococcus aureus	28	(45.9)
Haemophilus influenzae	7	(11.4)
Coagulase-negative Staphylococcus	5	(8.1)
Streptococcus viridans	4	(6.5)
Candida	3	(4.9)
Aspergillus	1	(1.6)
Mycobacterium tuberculosis	1	(1.6)
Other gram-negatives: Enterococcus faecium, Enterococcus faecalis, Chryseobacterium indologenes, Proteus mirabilis, Pandoraea, Morganella morganii, multisensitive Pseudomona aeruginosa (2) multiresistant (1), Klebsiella pneumoniae (2), Serratia marcescens (2), Moraxella catarrhalis (3), Escherichia coli (3), Klebsiella oxytoca (3), Enterobacter aerogenes (3)	25	(40)
Other gram-positives: Propionibacterium acnés, Streptococcus pyogenes (3), Streptococcus pneumoniae (2), Corynebacterium (3), methicillin-resistant Staphylococcus aureus (2)	11	(17.6)

Posttransplant infections are jointly one of the most common and most severe complications of a transplantation.(3) The purpose of the patient's screening is the identification of active and latent infections that might pose a risk for the recipient and include: clinical examination, epidemiologic inquiry and lab tests[3].

The tests used to detect infectious diseases are those recommended for every organ donor by the Organ Procurement and Transplantation Network (OPTN) and for organ recipients[4].

Unexpected disease transmissions are defined as the transmission of a pathogen from the donor to the recipient, despite donor selection to discard the presence of an infection. They can occur due to

TABLE 5. Donor-associated infection: characteristics and clinical outcome

	Case 25	Case 31
Age	65 years	30 years
Gender	Female	Male
Prioritization	Emergency	Emergency
Type	Single-lung	Double-lung
Retransplantation	No	No
Germ associated with the infection	Candida sp.	Multiresistant PAE
Type of infection	Septic shock: SSTI and pneumonia	Pneumonia
Deceased	Yes(2 months)	No (18 months)

SSTI: skin and soft tissue infections

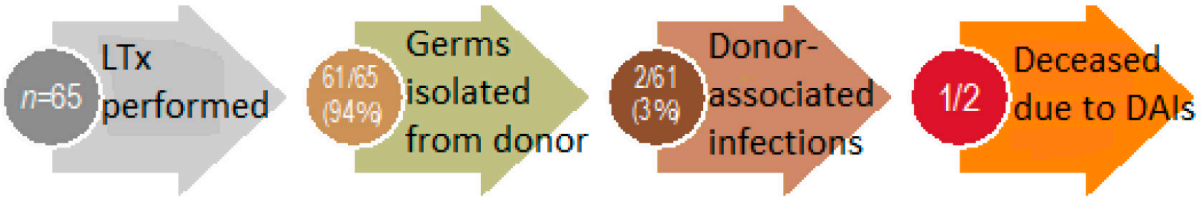

Figure 2. Clinical evolution after lung transplantation in terms of donor-associated infections

the donor's incomplete or inexact information, or failure of communication or the system, if the donor has acquired the infection recently and is still in the eclipse period or the serologic window period, or if the donor is infected with a rare or emergent pathogen not included in standard detection protocols. Unexpected transmissions are more likely to occur in the context of a deceased donor; however, they may also occur in the transplant of a living donor[2].

The course of posttransplant infections is divided in three periods related to the risk of infection with specific pathogens: **First month after transplantation:** could be caused by preexistent infection of the donor or recipient and infectious complications of the transplantation surgery and hospitalization. The main effects of exogenous immunosuppression are still not clear.(5) **1 to 6 months after transplantation:** there is usually the maximum effect of immunosuppression and the patients have higher risk of developing opportunistic infections. However, there may be residual problems of the perioperative period. Prophylaxis delays but doesn't eliminate the risk of infections that may occur months after prophylaxis is over[5]. **More than 6 to 12 months after transplantation:** most patients receive stable and reduced levels of immunosuppression. These patients are subject to community-acquired pneumonias caused by respiratory viruses, pneumococcus, Legionella or other common pathogens. The "late cytomegalovirus (CMV)" might occur in patients who received prophylaxis during the first three to six months[5].

Epidemiology of posttransplant infections

The rate of bacterial infections in lung and heart transplants (mainly respiratory infections) is much

higher than that observed in other recipients of solid organ transplants (SOTR). [6] Transmission of bacteria through the graft is very common in LTx, showing bronchial colonization even in 50% of the cases . However, it is very rare in other SOTRs in whom the transplanted organ is usually sterile[7].

Basing on available data from the USA and France, donor-derived diseases are transmitted in less than 1% of transplants in general[4]. The mortality rate as a consequence of DAIs in transplants in general, was 22%[2]. The incidence of DAIs during the first 2 postoperative weeks has decreased markedly because of antibiotic prophylaxis; most bacterial pneumonias occur in the intermediate (< 6 months) and late postoperative period (> 6 months). The overall cumulative incidence during the first year after transplantation is ~70% and it remains high beyond the first year (30%-40%). Nearly three-quarters of all bacterial pneumonias are caused by Pseudomonas species and Enterobacteriaceae, and the remainder primarily by Staphylococcus aureus, Enterococcus species and Hemophilus influenzae[8, 9]. In our series, the main isolated germs were methicillin-sensitive Staphylococcus aureus, 45.9%; Haemophilus influenzae, 11.4%, and coagulase-negative Staphylococcus, 8.1%.

The second most common infectious complication after LTx is CMV disease. The reported incidence without prophylaxis in larger series ranges between 53% and 75%[6]. In our transplantation program, prophylaxis for high-risk patients includes treatment with valganciclovir for no less than 6 months and sequential controls with plasma PCR (polymerase chain reaction) for the detection of CMV.

Invasive infections with Candida species occur during the first postoperative month, and most of them are transmitted through the donated organ. The most common presentations are candidemia, necrotizing bronchial anastomotic infection, mediastinitis and infection and disruption of aortic anastomosis after heart-lung transplantation[8, 10]. In our series, one of the two patients who developed a DAI died due to a septic shock secondary to a skin and soft tissue infection of the surgical wound and pneumonia caused by candida sp. with no response to treatment with azoles with susceptibility testing and adequate plasma concentrations. Heavy growth of Candida species in the donor bronchus is a significant obstacle for accepting the organs for transplantation. The sequelae are mediastinitis, sepsis, or involvement of the great vessels leading to mycotic aneurysms and consecutive rupture. In one series, 3 of 4 lung transplant recipients with heavy growth of Candida species developed mediastinitis, which was uniformly fatal[11].

There are different modes of transmission of infection by Mycobacterium tuberculosis in this population[3]: as reactivation of previous infection, primoinfection, exogenous reinfection and infection transmitted by the transplanted organ. In approximately 6% of LTx recipients, the mean posttransplant interval in which Mycobacterium tuberculosis is detected is 115 days. In 40% of the cases, the diagnosis was obtained from explanted lungs[6]. In our series, we isolated a tuberculous granuloma: one of the donor grafts had an indurated lesion in the right upper lobe. Intraoperative exeresis was performed with subsequent bacteriological and anatomo-pathological isolation. In subsequent controls through fibrobronchoscopy and cultures, there wasn't any evidence of disease development in the recipient. In general, Mycobacterium tuberculosis screening isn't performed in deceased donors, but should be done in all living donors[4, 12]. Despite the immunosuppression, we observed and adequate response to antituberculous treatment and low incidence of adverse secondary effects[13]. Active tuberculosis (TB) in a donor is a contraindication to donation; if a deceased donor is believed to have tuberculosis, his/her organs shall not be used unless active TB infection can be definitively discarded[4, 12, 14].

Diagnostic considerations

As part of our lung transplant program institutional protocol, a patient who is undergoing immediate postoperative clinical or radiological signs of infection receives a fibrobronchoscopic examination with bronchoalveolar lavage (BAL) and, in cases of transbronchial biopsy (TBB), the diagnostic yield is almost 70%[15]; it also allows for the inspection of the airways, which may reveal anastomotic problems or tracheobronchial aspergillosis. The bacteriological examination of bronchial lavages of the donor lung is a prerequisite for the treatment of subsequent invasive infection in transplant recipients, even the growth of normal oral flora in the donor is considered to be a risk factor for early bacterial pneumonia in the recipient.

The BAL is very sensitive to most pathogens, the TBB is the only means to diagnose acute rejection and pneumonitis caused by CMV[16]; its sensitivity and specificity is almost 100%. Computed tomography can be useful for the differential diagnosis of bilateral infiltrative lung diseases and detect bronchial, mediastinal or vascular complications[17].

Most centers now perform routine surveillance bronchoscopies after lung transplantation. Besides the early detection of asymptomatic episodes of significant acute rejection or CMV pneumonitis in ~20% -30% of procedures, it allows the early identification of cases colonized by Aspergillus.[8]

Review of previous works that document donor-associated infections in LTx recipients.

There is little literature about cases of DAI in lung transplant recipients. In this review, there were 3 studies that showed statistics which allowed us to compare our experience. Ruiz I et al.[18] evaluated recipients who survived more than 24 hours and their respective donors. The global incidence of donor infections was 52% (103 out of 197 donors). The types of donor-associated infections were contamination isolated in preservation fluids (n = 30, 29.1%), graft colonization (n = 65, 63.1%) and bacteremia (n = 8, 7.8%). Donor infection rates weren't statistically different between patients who received mechanical ventilation for 48 hours and those who received less or more than 48 hours. There were bacterial or mycotic DAIs in 15 LTx (7.6%). In this experience, 25% of donors with bacteremia and 14.1% of colonized grafts were responsible for the transmission of the infection. Two patients died from a DAI. Microorganisms for which it is very difficult to design effective prophylactic regimens that caused infection were Aspergillus fumigatus, Stenotrophomonas maltophilia and MSSA. Excluding these cases, failure of prophylaxis occurred in 5.6% of procedures.

Low et al[19] reported that in 28 out of 29 bronchial lavages from donors grew at least one microorganism. Microorganisms most frequently identified were Staphylococcus spp. and Enterobacter spp. In 43% of the cases, similar microorganisms were isolated from the recipient tracheobronchial tree, 21% of which had a DAI. Waller et al[20] made a retrospective comparison of the result of 123 donors in 125 consecutive lung or heart transplants with technical success. The microbial contamination of the routine bronchial lavage of the donor was nearly 60%. Five lung transplant recipients died because of a DAI.

Characteristics of antibiotic treatment

There aren't any guidelines or standardized regimens regarding the choice of the perioperative antibiotic therapy. Antibiotic prophylaxis in LTx recipients shall be initiated with broad-spectrum antimicrobial agents in order to cover gram-negatives and gram-positives.

We recommend that antibiotic coverage in lung transplant recipients should be initiated with a broad-spectrum agent and modified on the basis of cultures obtained from the donor[19]; in our transplantation program we use vancomycin and ciprofloxacin for non-colonized recipients with non-septic diseases who hadn't been hospitalized during the last month, except for patients with septic lung disease (cystic fibrosis or bronchiectasis) who must receive antimicrobial agents adapted to their pretransplant cultures for at least 2 weeks[4]; all of these guidelines subsequently adjusted to the isolates obtained. In one series, this approach reduced the incidence of early postoperative bacterial pneumonia from 33% in a historical control group to 13% ($p = 0.005$)[11].

In our program, according to the recommendation of the experts, we indicate nebulized tobramycin or colistin once the patient arrives at the ICU after surgery as prophylaxis in recipients that show previous gram-negative colonization. The duration of the prophylaxis depends on the results of the cultures of respiratory samples obtained from the donor and recipient at the moment of the LTx. If the cultures are negative, the prophylactic antibiotic agents are removed from the third to the fifth day; if they are positive, or in cases of recipients with septic pulmonary disease, the antibiotic treatment is adjusted and maintained for 2 weeks or until the cultures are negative.

With this approach, whenever a clinically significant microorganism is isolated in a respiratory sample within the first 3 months, a specific intravenous antibiotic therapy is initiated, even if the patient is asymptomatic. The only situations in which the treatment shall not be initiated are colonization by oral streptococcus or CoNS[6].

Conclusion

Donor-derived diseases are increasingly being recognized as causes of morbidity and mortality that occur usually during the early posttransplant period. Bacterial infection is the most common infectious complication in LTx recipients. Of all the lung transplantations performed in our series (n= 65), at least one germ was isolated in 61/65 (94%) biological samples collected from the donor. The main species isolated from donor cultures were methicillin-sensitive Staphylococcus aureus, Haemophilus influenzae and coagulase-negative Staphylococcus, mainly in preservation liquid, 78.6%; donor secretions, 73.7%; and only 3 cases showed bacteremia in the donor (4.9%). The rate of bacterial infections in lung and heart transplants (mainly respiratory infections) is much higher than that observed in other SOTR.

The prevalence of DAIs in LTx recipients in our series was 3.1%, higher than the figures documented in solid organ transplants in general (< 1%) but lower than the numbers found in the few published reports about LTx (7.6%).(18) One of the 2 cases with identified DAI died after developing septic shock secondary to pneumonia and a skin and soft tissue infection of the surgical wound with isolation of candida, with no response to treatment with azoles.

A high OS was observed; thus, there was low mortality associated with the LTx. It is possible that the use of prophylactic measures when selecting the suitability of the donor pulmonary graft and of antibiotic prophylaxis guidelines in recipients has a strong impact on such OS.

Recommendations

Regarding the management of the pulmonary graft, we recommend the following routine:

Send a sample of the preservation solution in which the organ was received for culture. Request culture results and take appropriate measures regarding the recipients. The possibility of a DAI shall be considered in all early infections and patients with atypical clinical courses.

The DAI is a common event after lung transplantation with fatal consequences that could be avoided with an adequate prophylactic antibiotic regimen that has to be modified according to the type of microorganisms isolated from the cultures of samples obtained from donors, grafts, preservation fluids and recipients.

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