Donor-derived bacterial infections in lung transplant recipients in the era of multidrug resistance

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Highlights:

- We used a tailored preventive antibiotic strategy to avoid donor derived infection.
- Multidrug-resistant (MDR) bacteria were isolated from 12/243 (4.9%) lung donors.
- None were transmitted to the recipients after our preventive antibiotic strategy.
- The lungs of donors colonized with MDR bacteria may be safely used.

Donor-derived bacterial infections in lung transplant recipients in the era of multidrug resistance

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ABSTRACT:

Objectives: Our aim was to analyze the prevalence of multidrug-resistant bacterial infections in lung transplant donors and to evaluate its influence on donor-derived bacterial infections.

Methods: We conducted a retrospective study of adult patients who underwent lung transplantation (2013-2016) at our hospital. Donor-derived bacterial infection was defined as the isolation of the same bacteria with identical antibiotic susceptibility patterns in the recipient and the perioperative cultures from the donor during the first month posttransplantation. We utilized a preventive antibiotic strategy adapted to the bacteria identified in donor cultures using systemic and nebulized antibiotics.

Results: 252 lung transplant recipients and 243 donors were included. In 138/243 (56.8%) donors, one bacterial species was isolated from at least one sample; graft colonization (118/243; 48.6%), blood cultures (5/243; 2.1%) and the contamination of preservation fluids (56/243; 23%). Multidrug-resistant bacteria were isolated from 12/243 (4.9%) donors; four Enterobacterales, four *Stenotrophomonas maltophilia*, three *Pseudomonas aeruginosa* and one methicillin-resistant *Staphylococcus aureus*. There was no transmission of these multidrug-resistant bacteria. Donor-derived infections, primarily tracheobronchitis due to non-MDR bacteria, were diagnosed in 7/253 (2.9%) recipients, with good clinical outcomes.

Conclusions: The lungs of donors colonized with multidrug-resistant bacteria may be safely used when recipients receive prompt tailored antibiotic treatment.

1 INTRODUCTION:

Donor-to-host transmitted infections pose a challenge in the safety of solid organ transplantation.[1] The lung is the solid organ with the highest probability of carrying a bacterial pathogen[2]. The lung is also the main site of donor colonization or infection, such as pneumonia[2]. We previously analyzed the incidence of donor-to-host transmitted infections in 210 lung transplant recipients between 1994 and 2002[3]. Although 52% of donors had an infection, only 12 (5.7%) recipients were diagnosed with donor-derived bacterial infections (DDBI). The low transmission rate was probably due to the tailored preventive antibiotic strategy used in these patients [3,4].

Currently, the scenario of bacterial infections has changed due to the emergence of multidrug-resistant (MDR) bacteria[5,6]. According to the European Center for Disease Prevention and Control (ECDC) the current levels of methicillin resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL) producing Enterobacterales and carbapenem resistant (CR) *Acinetobacter baumannii* in Spain are high and are above the European Union average[7]. The emergence of MDR bacteria can lead to the failure of routine antibiotic prophylaxis and transmission of donor infection[1]. There have been several reports of donor-derived MDR bacterial infections, some of them with fatal outcomes[8–13]. However, few studies have focused on donor MDR infection and the influence of donor MDR infection on recipient transmission in lung transplant cohorts. Accordingly, there are no specific recommendations regarding the use of organs colonized by MDR bacteria in the American and European guidelines[14,15]. Nonetheless, a careful risk-benefit analysis in donors with MDR infections is recommended.

Our aim was to analyze the prevalence of multidrug resistant bacteria infection in lung transplant donors and to evaluate its influence on donor-to-host transmission of infection.

2 MATERIAL AND METHODS:

2.1 Study population and study design: We conducted a retrospective study of all adult patients (> 16 years) who underwent lung transplantation from January 1, 2013 to December 31, 2016 at Vall d' Hebron University Hospital in Barcelona, Spain. Our institution is the leading lung transplant center in Spain. Since 1990 more than 1000 lung transplant procedures have been performed. Patients who died from non-infectious complications within 48 hours after transplantation were excluded from the study.

The Clinical Research Ethics Committee of our hospital approved the study (PR (IR) 70/2017) and waived the requirement for informed consent.

2.2 Lung transplant preparation and postoperative care: A standardized protocol for antibiotic management in lung transplant recipients has been developed in our center. The preventive antibiotic strategy includes intravenous amoxicillin-clavulanate 2 grams every 3 hours and ceftazidime 2 grams every 3 hours during the surgical procedure. We decided to use these dosages based on the short half-life of these drugs[16]. After the surgical procedure, the antibiotic treatment is intravenous amoxicillin-clavulanate 2 grams every 8 hours and ceftazidime 2 grams every 8 hours until we receive the results of perioperative cultures. After reviewing pretransplant isolated microorganisms, the preventive antibiotic strategy is adapted according to the antibiotic susceptibility pattern. This preventive antibiotic strategy is individually adapted in lung transplant candidates by a team of transplant infectious diseases physicians. In cases with recipient and/or donor positive intraoperative cultures antibiotic treatment is tailored and extended for 10 to 14 days and nebulized antibiotic with tobramycin (300mg every 12 hours) or colistin (2-5 million units every 8 hours) is added according to the antibiotic susceptibility pattern during at least the first 4-8 weeks after transplantation.

The baseline immunosuppressive regimen begins with an intravenous dose of 500 mg of methylprednisolone during the surgical procedure prior to lung reperfusion. The maintenance treatment consists of tacrolimus at doses that maintain blood levels of 10-15 ng/mL, and methylprednisolone (1 mg/kg/day for the first five days followed by 0.3 mg/kg/day) as

standard postoperative immunosuppressive therapy. Mycophenolate mofetil 1 to 2 grams per day is started on day five posttransplantation.

After transplantation, lower respiratory tract samples are taken when patients have purulent secretions or, clinical signs or symptoms of infection or every time a bronchoscopy is performed. We regularly performed one post-transplant bronchoscopy with bronchial aspirate collection, bronchoalveolar lavage and transbronchial biopsy in clinically stable patients between days 14-28 post-transplantation; the bronchoscopy was always performed before the patient was discharged from the hospital.

2.3 Microbiological cultures: Our protocol includes routine culturing of bronchial aspirate, blood cultures, and preservation fluid samples from all donors. Blood sampling is performed prior to organ removal. Immediately prior to the implantation, preservation fluid samples are taken, and a selective and protected bronchial aspirate is performed after opening the bronchial suture from the lung graft. In bilateral lung transplants, the same procedure is performed in both grafts. A selective and protected bronchial aspirate is also performed from explanted lungs. Gram stain results are available within one hour and the preliminary results of cultures are available in 24 hours. Blood cultures are incubated in an automatic system for 7 days. Semiquantitative and qualitative cultures of bronchial aspirates and preservation fluid are plated in standard microbiological media and incubated for 48 hours.

Antimicrobial susceptibility was determined by disc diffusion and for selected antimicrobials and/or when the zone diameter was close to the breakpoints values, MIC gradient strip test (Etest, bioMérieux, Marcy l'Étoile, France) was performed following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations (version 3.1 to 6.0 available from: http://www.eucast.org/ clinical–breakpoints/). Detection of ESBLs in Enterobacterales was based on non-susceptibility to cefotaxime or ceftazidime, and synergy between clavulanate and at least one of the following antibiotics: cefotaxime, ceftazidime, aztreonam and cefepime. Evidence suggestive of carbapenemase production was determined using EUCAST screening cut-off values (disk inhibition zones of <25 mm for

meropenem and <25 for ertapenem; or MICs > 0.125 mg/L for meropenem and/or ertapenem). Additionally, phenotypic testing for carbapenemase production, including Modified Hodge test, temocillin susceptibility and double-disk synergy test method with meropenem combined with boronic acid, cloxacillin or dipicolinic acid, was performed on isolates with suggestive production of carbapenemase [17]. If phenotypic testing was positive, the presence of the genes encoding carbapenemases OXA-48-like, KPC, VIM, IMP, IMI, and NDM were screened by PCR as previously described [18]. For *Stenotrophomonas maltophilia,* EUCAST guidelines were followed to evaluate the susceptibility to trimethoprim-sulfamethoxazole and Clinical & Laboratory Standards Institute (CLSI) recommendations were applied to evaluate susceptibility to ceftazidime, tetracyclines and levofloxacin. Additionally for *S. maltophilia,* colistin susceptibility was performed and interpreted according as suggested by the CLSI for *Pseudomonas aeruginosa* [19].

2.4 Definitions: Donor-to-host transmission of infection was defined as the isolation of the same microorganism in the recipient and the perioperative cultures from the donor during the first month posttransplantation when the isolates presented the same antibiotic susceptibility pattern.

Donor infection was defined as the existence of bacteremia, graft colonization and/or the isolated contamination of preservation fluids. Bacteremia was defined as any blood culture positive for bacteria. Lung graft colonization was based on the isolation of any amount of bacteria in bronchial aspirates. Bacteria of difficult to interpret pathogenicity such as coagulase negative staphylococci, *Cutibacterium acnes* and *Neisseria* spp. were not considered in the study. The isolated contamination of preservation fluids occurred when bacteria were isolated only in the preservation fluids.

Tracheobronchitis and pneumonia (proven and probable) were defined according to the International Society of Heart and Lung Transplant (ISHLT) consensus definitions for cardiothoracic transplant recipient infections[20]. Tracheobronchitis was diagnosed if one microbiological criterion and at least one of the two following clinical criteria were fulfilled: (1)

New-onset purulent sputum, a change in characteristics/quantity of sputum or an increase in the amount of suctioned respiratory secretions or (2) new-onset or worsening cough, dyspnea, tachypnea and the presence of one or more endobronchial lesions (erythema, ulceration, necrosis and pseudomembrane formation) without an alternative diagnosis and without evidence of invasive parenchymal disease. The microbiological criterion was the presence of at least one positive respiratory culture (sputum, bronchial secretions or bronchoalveolar lavage). Tracheobronchitis was classified as proven if there was a histopathological evidence of inflammation with organisms or a positive culture from the lung parenchyma. In cases with no histopathological evidence, tracheobronchitis was classified as probable. The definition of tracheobronchitis required the absence of radiographic consolidation in chest X-rays or CT scans. The definition of pneumonia required the presence of a new radiographic consolidation.

MDR bacteria were defined as having acquired nonsusceptibility to at least one agent in three or more antimicrobial categories. Extensively drug resistant (XDR) bacteria were defined as having nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories according to established criteria[21]. These definitions were used for *S. aureus*, Enterobacterales and *Pseudomonas aeruginosa*. Other nonfermenting gram-negative bacteria, such as *Stenotrophomonas maltophilia*, are intrinsically resistant to most antibiotics[22]. Despite the lack of established criteria to define MDR in these bacteria, *S. maltophilia* was considered a MDR microorganism for the purpose of the study.

2.5 Data collection: Electronic health records were reviewed for clinical data, antibiotic duration and outcomes of lung transplant recipients. Medical records were reviewed according to a pre-established protocol and data was entered in a specific database. All culture and microscopic examination results were automatically registered. Data from donor and recipient cultures were retrieved from the Microbiology Department database system. Donor epidemiological information, underlying diseases, cause of death and duration of premortem mechanical ventilation were also registered.

Two transplant infectious disease physicians (I.L. and O.L.) independently evaluated all possible donor to host transmission cases and defined the recipient infection according to ISHLT consensus definitions. In cases of disagreement, a third transplant infectious diseases physician (J.G.) was consulted. The recipients of a donor-to-host transmitted infection were followed for six months to assess the outcome of the infection.

2.6 Statistical analysis: Qualitative variables were reported as frequency (percentages) and quantitative variables as the means with standard deviation or median and interquartile ranges (IQR) or range. Associations between categorical variables were determined via Fisher's exact tests. A two sided p-value of < 0.05 was considered significant. Statistical analyses were performed with IBM SPSS software, version 21.0 (IBM Corp, Armonk, NY, USA).

3 RESULTS:

3.1 Patient characteristics

During the study period, 268 lung transplant procedures were performed in our hospital. After excluding 12 pediatric recipients and 4 recipients who died during the first 48 hours, 252 lung transplant recipients were included. The primary clinical characteristics are shown in Table 1. In all, 243 donors were included in the study. A single lung was transplanted to 18 different recipients from nine donors. Thirty-eight of 243 (15.6%) donors were from our hospital, 204/243 (84.0%) were from 58 hospitals in Spain and there was one donor from a Swiss hospital. Details of donors' demographic characteristics are shown in Table 2.

3.2 Description of isolated bacteria in donors' samples

The overall prevalence of donors with at least one bacterial isolation was 138/243 (56.8%). Descriptions of isolated bacteria from each sample are presented in Table 3. Of 118 donors with positive bronchial aspirate cultures, one also presented with positive blood cultures for the same bacterial species (*Hafnia halvei*) and 31/118 (26.3%) had the same bacteria isolated in the preservation fluid. The most common isolated species was *S. aureus.*

Only five donors had positive blood cultures. The most common isolated microorganism was *E. coli*. Fifty-six donors presented with bacteria that had been isolated from preservation fluid cultures: 31/56 (55.4%) with the same bacteria in bronchial aspirate, 9/56 (16.1%) with different bacteria in bronchial aspirate or blood cultures and 16/56 (28.6%) with no other bacteria in other samples. The most common isolated species was *S. aureus.*

3.3 Multidrug resistant bacteria in donors' samples

Multidrug resistant bacteria were isolated in 12/243 (4.9%) donors; 11/12 (91.7%) cases included graft colonization and two of them had positive preservation fluid cultures. In one case, isolated preservation fluid culture was present. The most common isolated MDR bacteria were nonfermenter gram-negative bacilli in 7 cases (4 *S. maltophilia* and 3 *P. aeruginosa*), Enterobacterales in 4 cases and methicillin resistant *S. aureus* in one case. Eight out of twelve (66.7%) donors colonized with MDR bacteria and 70 out of 226 (31%) non-MDR colonized donors were mechanically ventilated for more than 48 hours (p=0.02). There were no differences in the prevalence of MDR donor infection related to the cause of donor death. Clinical and microbiological data of donors with isolation of MDR bacteria are shown in Table 4.

In two cases, isolated bacteria were susceptible to regular prophylaxis at our hospital (ceftazidime). The other 10 donor lungs were transplanted to eleven recipients. In 5 recipients, intravenous antibiotic prophylaxis was changed to an active antibiotic in a median timeframe of 2 days (range 1-3 days). In five of the remaining six recipients with no change in intravenous antibiotic prophylaxis, nebulized antibiotics were used. The type and duration of antibiotic prophylaxis in each recipient are detailed in Table 4. There were no cases of donor to host transmission of MDR bacteria.

3.4 Donor-to-host transmission

In seven of 253 (2.9%) recipients, a DDBI by non-MDR bacteria was detected a median of ten days (range 1-32) after the transplant procedure. Microbiological and clinical data of the

donor-to-host transmission of bacterial infection are shown in Table 5. Polymicrobial transmission (*H. influenzae* and *S. aureus*) occurred in one case and the other cases were monomicrobial transmissions: *P. aeruginosa* in two cases, and *Klebsiella pneumoniae*, *Serratia marcescens*, *Streptococcus pneumoniae* and *S. aureus* in one case each. Five patients were diagnosed with proven or probable tracheobronchitis, one case of proven pneumonia and one case of *S. aureus* bacteremia. All recipients were treated with adequate antibiotics and exhibited good clinical outcomes.

5 DISCUSSION

In this recent cohort of lung transplant recipients, almost 60% of donors presented with perioperative infection. However, only seven (2.9%) recipients were diagnosed with DDBI, mainly tracheobronchitis, with a good clinical outcome. Of interest, only 12/243 (4.9%) donors presented with MDR bacteria and no infections were transmitted to the recipients.

Regarding DDBI, a 49% decrease in the number of cases was observed compared to our previous study (2.9% vs 5.7%)[3]. In our previous study, two different antibiotic prophylaxis protocols were used during the study period, namely, cefuroxime 1.5 g/8 h (1990–1996) and amoxicillin-clavulanate 2 g/8 h plus aztreonam 1 g/8 h (1997–2002). Starting in 2009, we stopped using aztreonam and switched to ceftazidime due to the limited availability of aztreonam in our center. DDBI rates in lung transplant recipients are slightly higher in other studies. In a study performed between 1998 and 2001 at John Hopkins Hospital, 5 of 80 (6.25%) DDBI were described, some with a fatal outcome[23]. In a French study from 2006 to 2012, 12 of 175 (6.8%) lung transplant recipients presented with DDBI [24]. However, there were no data about the antibiotic susceptibility patterns of the isolates and the antibiotic duration was not described[24]. We believe that the low rate of DDBI in our study is mainly due to the standardized preventive antibiotic strategy used in our center.

There are very few studies describing the epidemiology of donors with MDR bacteria. In a single center Italian study, 10.5% of 170 donors presented with colonization or infection due to CR gram-negative bacteria[25]. In a multicenter Italian study that included the active surveillance of colonization[26], 3.6% of 111 lung transplant donors presented with CR Enterobacterales colonization. These data show a greater prevalence of CR Enterobacterales in transplant donors compared with our study results. Although we encountered four cases of MDR Enterobacterales, none of them was CR. This could be due to the different epidemiology of MDR bacteria in both countries. In Italy an increase of CR *K. pneumoniae* occurred, reaching 33% of *K. pneumoniae* isolates in bacteremia in 2014-2015[26]. On the other hand, the XDR *P. aeruginosa* isolates in our study were CR and two were VIM carbapenemase producers. To the best of our knowledge, there are no previous reports of lung transplant donors colonized with MDR or XDR *P. aeruginosa*.

Several cases of donor-to-recipient transmission of gram-negative MDR bacteria have been reported[11], but only a few in lung transplant recipients[25–28]. Data regarding infection transmission in lung transplant donors colonized with MDR bacteria are limited to three studies that analyzed CR gram-negative bacteria. In the first study[25], only three lung donors were colonized with CR gram-negative bacteria (two *A. baumannii* and one *K. pneumoniae*). None of the two recipients of donor tissue colonized with CR *A. baumannii* developed a donor-derived infection, and one did not receive active antibiotics. The recipient of tissue from a bacteremic donor with CR *K. pneumoniae* did not receive targeted antibiotics and donor-to-host transmission was reported. However, the recipient only presented with airway colonization. These results are contrast with those reported in a recent Italian study of 119 lung transplant recipients[26]. Four donors were colonized with CR Enterobacterales, which were transmitted to three recipients. One of the recipients died at day nine due to early transplant failure and the others were alive at day 28. However, clinical data are limited and there is no information about antibiotic prophylaxis in these cases. In the last study, an observational nationwide Italian study, three lung recipients received an organ colonized by

CR Enterobacterales [29]. One of them presented early post-transplant sepsis due to the same Enterobacterales species and died. Once again, there is no information about antibiotic prophylaxis in these cases.

In our study, MDR bacteria in donors were primarily gram-negative bacteria. In two of eleven cases, bacteria were susceptible to our regular preventive antibiotic strategy. In three of nine cases, intravenous antibiotic treatment was tailored according to the isolated bacteria. Nonetheless, in the other six recipients with inadequate intravenous antibiotic therapy, there was no transmission of infection. These could be due to several different reasons. Four of these six cases were due to *S. maltophilia*, a bacteria species with lower pathogenicity than Enterobacterales or *P. aeruginosa*; this lower pathogenicity could influence the lack of transmission. Additionally, nebulized antibiotics could have prevented the transmission of infection in these cases in bacteria susceptible to the nebulized antibiotics. There are few published studies about nebulized antibiotics in lung transplant recipients, but most centers use them in regular practice[6]. Nebulized antibiotics allow for the maximization of epithelial lining fluid concentrations while minimizing systemic exposure and toxicity. The use of targeted nebulized antibiotic therapy can be considered in this setting based on our results.

A few cases of donor-derived MRSA infection have been reported and only one infection has been described in lung transplant recipients[11,30]. A lung transplant recipient received vancomycin at the time of transplantation due to donor premortem blood cultures positive for MRSA [30]. Six days after transplantation the recipient blood cultures and bronchoalveolar lavage cultures were positive for MRSA and required prolonged antibiotic therapy. In our study, one donor presented with MRSA graft colonization and neither of the two recipients developed an infection after the antibiotic prophylaxis was changed to linezolid.

Our study has some limitations, including those inherent to a single-center and retrospective study. However, a large cohort of lung transplant recipients who received uniform management was analyzed. Moreover, a cohort of donors from 60 different hospitals with different antibiotic policies were included in the study. Second, these results may be not

generalized to countries with a higher prevalence of MDR bacteria. Third, due to the retrospective nature of this study, we could not perform strain typing or whole genome sequencing of these bacteria; thus, some cases of DDBI could have been acquired after the transplantation. Although this could lead to an overestimation of donor transmitted bacterial infections, the prevalence of DDBI in our study is very low. Fourth, information about donor cultures obtained before death was not available in many cases. Nonetheless, this is the most common scenario in daily clinical practice, since donor colonization by MDR bacteria is not usually known until the transplant procedure.

In conclusion, we found a low prevalence of MDR bacterial infection in lung donors with no transmission of infection. In our opinion, donor tissue that has been colonized with MDR bacteria could be safely used for lung transplantation when recipients receive tailored antibiotic treatment even when these antibiotics are given as nebulised administration.

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Table 1. Clinical characteristics of lung transplant recipients

Characteristics	**Recipients (n=252)**
Age, median [IQR] years	57 [49-61]
Male sex	149 (59.1)
Underlying diseases	
Pulmonary fibrosis	82 (32.5)
COPD	73 (29)
Pneumonitis	39 (15.5)
Cystic fibrosis	20 (7.9)
Bronchiectasis	12 (4.8)
Primary pulmonary hypertension	10 (4)
Others	16 (6.3)
Type of transplant	
Single lung transplant	86 (34.1)
Bilateral lung transplant	166 (65.9)

Data are presented as the number and percentage unless otherwise indicated.

IQR: interquartile ranges

Table 2. Clinical characteristics of donors

Characteristics	**Donors (n=243)**
Age, median [IQR] years	51 [42-59]
Male sex	132 (54.3)
Cause of death*	
Stroke	164 (67.5)
Head injury	36 (14.8)
Anoxia	29 (11.9)
Others	11 (4.5)

Mechanically ventilated*	
< 48 hrs	160 (65.4)
> 48 hrs	78 (32.1)

Data are presented as the number and percentage unless otherwise indicated.

*Missing values: cause of death (3), mechanically ventilated (5).

IQR: interquartile ranges

Table 3. Description of isolated bacteria in donor samples

	Bronchial aspirate	**Blood cultures**	**Preservation fluid cultures**
Number of donors with at least one bacteria isolated*	118/241(49.0)	5/237 (2.1)	56/240 (23.3)
GP bacteria	Total: 66/241 (27.4) positive samples with 66 GP bacteria isolated *S. aureus* 52 (21.4) *S. pneumoniae* 6 (2.5) Other GP bacteria 8 (3.3)	Total: 1/237 (0.4) positive samples *S. aureus* 1 (0.4)	Total: 33/240 (13.8) positive samples with 35 GP bacteria isolated *S. aureus* 13 (5.4) *Streptococcus* spp. 12 (5) Other GP bacteria 10 (4.2)
GN bacteria	Total: 73/241 (30.3) positive samples with 87 GN bacteria isolated *P. aeruginosa* 14 (5.8) *E. cloacae* 14 (5.8) *H. influenzae* 11 (4.6) *K. pneumoniae* 11 (4.6) *S. macescens* 10 (4.1) *E. coli* 6 (2.5) *P. mirabilis* 5 (2.1) *S. maltophilia* 3 (1.2) *A. baumannii* 1 (0.4) Other GN bacteria 14 (5.8)	Total: 4/237 (1.7) positive samples *E. coli* 2 (0.8) *Hafnia alvei* 1 (0.4) *Eikenella corrodens* 1 (0.4)	Total: 29/240 (12.1) positive samples with 32 GN bacteria isolated *H. influenzae* 8 (3.3) *S. macescens* 5 (2.1) *E. cloacae* 4 (1.7) *E. coli* 3 (1.3) *P. aeruginosa* 2 (0.8) *S. maltophilia* 2 (0.8) *K. pneumoniae* 1 (0.4) Other GN bacteria 7 (2.9)

Data are expressed as the number and percentage. *Bronchial aspirate was not available in 2 donors, blood cultures were unavailable in 6 donors, and preservation fluid cultures were unavailable in 3 donors.

CNS: Coagulase negative staphylococci; GN: gram-negative; GP: gram-positive

Case nº	Donor age (years)	Cause of death	Time of MV	Type of sample	Isolated bacteria	Antibiotic susceptibility pattern	Drug resistance mechanism	Susceptible to regular antibiotic prophylaxis (*1)	Change of intravenous antibiotic (days after LT) (*2)	Intravenous antibiotic prophylaxis and duration (days)	Nebulized antibiotic (type)	DDI

Table 4. Clinical and microbiological characteristics of donors with isolated multidrug resistant bacteria and their respective recipients

D1	40	Stroke	>48 hrs	BA	*P. aeruginosa*	Only S to COL and CAZ (XDR)		Yes	N/A	CAZ 12	COL	No
D2	32	Others	>48 hrs	BA	*P. aeruginosa*	Only S to COL and AMK (XDR)	VIM carbapenemase producer	No	No	CAZ 10 (*3)	COL	No
D3	59	Anoxia	>48 hrs	BA	*P. aeruginosa*	Only S to colistin (XDR)	VIM carbapenemase producer	No	No	CAZ 5	COL	No
D4	57	Stroke	>48 hrs	BA and PF	*S maltophilia*	Only S to COL, SXT, DOX and LVX		No	No	Meropenem 5 days and later CAZ 7 days more (*4)	COL	No
D5	20	Head injury	>48 hrs	BA	*S maltophilia*	Only S to COL, SXT and DOX		No	No	Meropenem 10 (*5)	No	No
D6	67	Head injury	<48 hrs	BA	*S maltophilia*	Only S to COL, SXT, DOX and LVX		No	No	CAZ 5	COL	No
D7	19	Head injury	>48 hrs	PF	*S maltophilia*	Only S to COL, SXT, DOX and LVX		No	No	CAZ 7	COL	No
D8	64	Stroke	<48 hrs	BA	*E. coli*	R to AMP, GEN and SXT		Yes	N/A	CAZ 6	No	No
D9	63	Stroke	<48 hrs	BA	*E. cloacae*	Only S to FEP, CB, AMG, CIP and COL	AmpC beta-lactamase hyperproduction	No	Yes (3)	Meropenem 14	COL	No
D10	55	Anoxia	>48 hrs	BA and PF	*Citrobacter braaki*	Only S to FEP, CB, AMG, CIP and COL	AmpC beta-lactamase production	No	Yes (1)	Meropenem 9	No	No
D11	52	Stroke	>48 hrs	BA	*P. mirabilis*	Only S to CB, AMG and CIP	ESBL beta-lactamase producer	No	Yes (3)	Meropenem 13	COL	No
D12	42	Stroke	<48 hrs	BA	*S. aureus*	R to MET, ERY and CIP		No	Recipient 1: Yes (2) Recipient 2: Yes (2)	Linezolid 10 Linezolid 13	No No	No No

AMK: amikacin; AMG: aminoglycosides; AMP: ampicillin; BA: bronchial aspirate; CAZ: ceftazidime; CB: carbapenems; CIP: ciprofloxacin; COL: colistin; DDI: donor-derived infection; DOX: doxycycline; ERY: erythromycin; FEP: cefepime; GEN: gentamicin; LT: lung transplant; LVX: levofloxacin; MV: mechanical ventilation; N/A: not applicable; PF: Preservation fluids; R: resistant; S: susceptible; TOB: tobramycin; SXT: trimethoprim-sulfamethoxazole; XDR: Extensively drug resistant.

(*1): The regular antibiotic prophylaxis in our hospital was intravenous amoxicillin-clavulanate and ceftazidime (section 2.2 of the manuscript).

(*2): In this column, we describe if the regular intravenous antibiotic prophylaxis was changed according to the isolated bacteria in donor's cultures.

(*3): The recipient was diagnosed with cystic fibrosis and chronically infected with ceftazidime susceptible *Pseudomonas aeruginosa.*

(*4): *Klebsiella pneumoniae* resistant to amoxicillin-clavulanate was also isolated in the donor bronchial aspirate.

(*5): The recipient was diagnosed with bronchiectasis and chronically infected with carbapenem susceptible *Pseudomonas aeruginosa*.

Table 5. Clinical and microbiological characteristics of non multidrug-resistant donor derived bacterial infections

Recipient number	Isolated bacteria	Positive samples in donors	Positive samples in recipients	Days post LT	Type and duration of prophylaxis	Type of infection	Clinical outcome
R1	*P. aeruginosa*	BA	Tracheal aspirate	32	Ceftazidime (11)	Proven tracheobronchitis	Good clinical outcome
R2	*P. aeruginosa*	BA and PF	BA	10	Ceftazidime (12)	Probable tracheobronchitis	Good clinical outcome
R3	*S. marcescens*	BA and PF	BA, BAL and pulmonary biopsy	9	Meropenem (8)	Proven pneumonia	Good clinical outcome
R4	*S. pneumoniae*	BA	BA and BAL	11	Amoxicillin-clavulanate (5)	Proven tracheobronchitis	Good clinical outcome
R5	*K. pneumoniae*	BA	Tracheal aspirate	15	Amoxicillin-clavulanate + ceftazidime (6)	Probable tracheobronchitis	Good clinical outcome
R6	Methicillin susceptible *S. aureus* and *Haemophilus*	BA and PF	Tracheal aspirate	1	Meropenem (8)	Probable tracheobronchitis	Good clinical outcome

	influenzae						
R7	Methicillin susceptible *S. aureus*	BA and PF	BC and tracheal aspirate	1	Initially, meropenem and later on cloxacillin (18)	Bacteremia and septic shock	Good clinical outcome. Negative BC after 72 hours of antibiotics

BA: bronchial aspirate; BAL: bronchoalveolar lavage; BC: blood cultures; LT: lung transplant; PF: preservation fluid.