

## Evaluation of donor-derived bacterial infections in lung transplant recipients

*Akciğer nakilli hastalarda donör ilişkili bakteriyel enfeksiyonların değerlendirilmesi*

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### ABSTRACT

**Background:** This study aims to evaluate the etiology and outcomes of donor-derived bacterial infections in patients undergoing lung transplantation.

**Methods:** Between January 2013 and December 2017, a total of 71 lung transplant recipients (56 males, 15 females; median age: 43.3 years) were retrospectively analyzed. The diagnosis of donor-derived bacterial infection was defined as the isolation of the same bacteria with the same antibiotic susceptibility patterns in a lung sample of donor and in one sample obtained from patients after transplantation and the presence of clinical evidence of infection.

**Results:** Ten (14%) patients were found to have donor-derived bacterial infection. *Acinetobacter baumannii* was found in three, *Pseudomonas aeruginosa* in three, *Klebsiella pneumoniae* in one, *Enterobacter cloacae* in one, *Staphylococcus aureus* in one, and both *Klebsiella pneumoniae* and *Acinetobacter baumannii* in one patient. Twenty-four of lung-transplant recipients and four patients with donor-derived infection died.

**Conclusion:** Lung transplants are usually performed in hospitalized patients or in those admitted to the intensive care unit. These patients commonly experience infection and colonization with resistant microorganisms.

**Keywords:** Donor-derived bacterial infection, lung transplant, multiple drug resistance.

Lung transplantation (LTx) is a widely accepted treatment that enhances the quality of life and prolongs survival of individuals with end-stage lung diseases. Despite advances in organ transplantation in recent years, the majority of transplant recipients may encounter a variety of challenges that should be overcome. Pneumonia has been reported to

### ÖZ

**Amaç:** Bu çalışmada, akciğer nakli yapılan hastalarda donör kaynaklı bakteriyel enfeksiyonların etiolojisi ve sonuçları değerlendirildi.

**Çalışma planı:** Ocak 2013-Aralık 2017 tarihleri arasında toplam 71 akciğer nakli alıcısı (56 erkek, 15 kadın; medyan yaş: 43.3 yıl) retrospektif olarak incelendi. Donör kaynaklı bakteriyel enfeksiyon tanısı, donör akciğer dokusu örneğinde ve nakil sonrası hastanın örneklerinden birinde aynı antibiyotik duyarlılık paternlerine sahip aynı bakterilerin izolasyonu ve klinik enfeksiyon kanıtının varlığı olarak tanımlandı.

**Bulgular:** On (%14) hastada donör kaynaklı bakteriyel enfeksiyon tespit edildi. Üç hastada *Acinetobacter baumannii*, üç hastada *Pseudomonas aeruginosa*, bir hastada *Klebsiella pneumoniae*, bir hastada *Enterobacter cloacae*, bir hastada *Staphylococcus aureus* ve bir hastada *Klebsiella pneumoniae* ve *Acinetobacter baumannii* bulundu. Akciğer nakli yapılan hastaların 24'ü ve donör kaynaklı enfeksiyonu olan hastaların dördü kaybedildi.

**Sonuç:** Akciğer nakli genellikle hastanede yatan veya yoğun bakım ünitesine kabul edilen hastalarda yapılmaktadır. Bu hastalarda dirençli mikroorganizmalara bağlı enfeksiyon ve kolonizasyon görülebilir.

**Anahtar sözcükler:** Donör kaynaklı bakteriyel enfeksiyon, akciğer nakli, çoklu ilaç direnci.

develop in up to 60.4% of patients in some series after LTx.<sup>[1]</sup> In these patients, the primary factors associated with the increased risk for pneumonia include pre-transplant colonization of the donor lung and the upper airways with pathogenic bacteria and post-transplant deterioration of the mucociliary activity due to ischemia and reperfusion injury

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in the immediate postoperative period, bronchial narrowing in the anastomosis area, and impaired cough reflex due to lung denervation.<sup>[2]</sup> The success of the LTx usually depends on prevention of early post-transplant complications such as primary graft failure (i.e., cellular and antibody-mediated rejection) and infections.<sup>[2]</sup> The lungs are the organs where donor infections such as pneumonia and colonization without signs of infection are common, with a high risk of carrying microorganisms.<sup>[3]</sup> Therefore, donor-derived infections are common in LTx patients.

In the present study, we aimed to evaluate the etiology and outcomes of donor-derived bacterial infections in patients undergoing LTx.

## PATIENTS AND METHODS

This single-center, retrospective study was conducted at Koşuyolu High Specialization Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology between January 1<sup>st</sup>, 2013 and December 31<sup>st</sup>, 2017. A total of 71 LTx recipients (56 males, 15 females; median age: 43.3 years) were included in the study.

Cultures from lung tissue were obtained during operation at the time of organ removal. Our protocol included donor and recipient blood cultures, the culture of preservation fluid of donor lung, the recipients' tracheal aspirate, and the culture from bronchoalveolar lavage fluid (BAL). Tissue samples were obtained from the lungs by selective and protected bronchial brushing before the graft removal. All patients were also screened for rectal carriage of vancomycin-resistant Enterococci (VRE) and carbapenem-resistant *Klebsiella* spp. All samples were evaluated in the microbiology laboratory of our hospital. Antibiotic susceptibility was studied by the VITEK-2® COMPACT System (bioMérieux, Marcy l'Etoile, France) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Cefazolin was used for preoperative prophylaxis.

Donor-derived infection was defined as the growth of the same microorganism as that in the donor lung sample, with the same antibiotic sensitivity, from the endotracheal aspiration, blood, sputum, and BAL cultures of the patient after transplantation, and the presence of fever, tachypnea, purulent respiratory secretion, increased secretion of the recipient, and signs of infection such as pathological findings on respiratory system examination.

Pneumonia was defined as a positive culture of BAL samples yielding  $\geq 10^5$  colony-forming units (CFU)/mL combined with new or persistent lung infiltrate on chest X-ray, and two or more of the following criteria: temperature  $\geq 38.4^\circ\text{C}$  or  $< 36^\circ\text{C}$ , a white blood cell (WBC) count of  $> 11,000/\text{mm}^3$  or  $< 4,000/\text{mm}^3$ , at least 30% decrease of partial pressure of oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio, and purulent secretions.<sup>[4]</sup>

## Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were presented in mean  $\pm$  standard deviation (SD) or median (min-max), while categorical variables were presented in number (n) and frequency (%).

## RESULTS

Sixty-two (87.3%) patients underwent bilateral LTx and nine (12.7%) patients right lobe LTx. Indications for LTx in our patients were as follows: interstitial lung disease (n=22, 30.9%), bronchiectasis (n=13, 18.3%), chronic obstructive pulmonary disease (COPD) (n=12, 16.9%) cystic fibrosis (n=8, 11.3%), and silicosis (n=4, 4.2%). Sixteen (22.5%) patients underwent extracorporeal membrane oxygenation (ECMO) after transplantation. Table 1 shows the demographic characteristics and transplant diagnoses of patients and types of transplants.

For LTx, donor lungs were obtained in the intensive care units (ICUs) of several hospitals in Türkiye (in training and research hospitals, 22 donors [30%], in private hospitals, 20 donors [27%], in public hospitals, 15 donors [20%], and in university hospitals, 14 donors [13%]) (Table 3).

After evaluating the specimens according to the criteria, 10 (14%) patients were identified to have donor-derived infection. *Acinetobacter baumannii* was found in three, *Pseudomonas aeruginosa* in three, *Klebsiella pneumoniae* in one, *Enterobacter cloacae* in one, *Staphylococcus aureus* in one, and both *Klebsiella pneumoniae* and *Acinetobacter baumannii* in one patient. The distribution of recipients' specimens with bacterial growth was as follows: seven BAL, one blood culture, one tracheal aspirate culture, and one sputum culture. The agents causing donor-derived infections in recipients are shown in Table 2. In addition, rectal carriage of carbapenem was detected in two patients and rectal carriage of VRE in three patients. Of 10 cultures of lung preservation fluid, two cultures grew microorganism, which was considered

**Table 1. Demographic and clinical characteristics of patients (n=71)**

	n	%	Median
<b>Patients characteristics</b>			
Age (year)			43.3
Sex			
Male	56		
Female	15		
<b>Underlying disease</b>			
Interstitial pulmonary disease	22	31	
Bronchiectasis	13	18.3	
COPD	12	17	
Cystic fibrosis	8	11	
Silicosis	4	5.6	
Sarcoidosis	3	4.2	
Other	9	12.7	
Total	71		
<b>Transplantation type</b>			
Bilateral	62	87.3	
Right lobe	9	12.7	
<b>Other treatment</b>			
ECMO	16	22.5	

COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation.

as contamination. The mean duration of hospital stay was 27.4±9.8 (range, 1 to 112) days. Of 10 patients, four (40%) developed donor-derived bacterial infections. The mortality rate of the patients was 20%. Of 71 screened donors, 38% (n=27) were colonized. While 90-day early mortality rate was 29.6% (8/27) in patients with donor colonization, it was 25% (11/44) in patients without donor colonization.

## DISCUSSION

Infection after LTx is the second most common cause of mortality within the first 30 days (19.2%) after transplantation, but is the most common (37.3%) cause between 30 days and the first year. Our patients underwent LTx most frequently for interstitial lung disease and bronchiectasis. We found that the lungs of donors were particularly colonized and/or infected with Gram-negative microorganisms. The swab cultures of the patients and the donor transport fluid should also be considered as a source of donor-associated post-transplant infections.

Although there are few studies evaluating perioperative antibiotics for LTx, randomized-controlled trials are still lacking. Retrospective studies have shown a reduction in post-transplant pneumonia in cases treated with antibiotic prophylaxis, but there is little guidance in the literature regarding specific regimens or their durations.<sup>[5]</sup> Therefore,

**Table 2. Infectious etiology of donor-derived bacterial infections**

Patient	Age/sex	Diagnosis	Infection agents	Day of the growth	Sample	Antimicrobial Sensitivity	Result
1	20/M	Bronchiectasis	<i>A. baumannii</i>	1	BAL	Col, GN, AK, TIG	Alive
2	44/M	Lung cancer	<i>K. pneumoniae</i>		BAL	All AB	Alive
3	55/M	IPF	<i>K. pneumoniae</i> <i>A. baumannii</i>	2	BAL	Col	Alive
4	57/M	IPF	<i>P. aeruginosa</i>	4	BAL	Col, tobramycin	Alive
5	55/M	COPD	<i>S. aureus</i>	1	BAL	MSSA	Alive
6	55/M	IPF	<i>P. aeruginosa</i>	1	BAL	Col	Dead
7	22/M	IPF	<i>E. cloaca</i>	2	Sputum	Col	Alive
8	41/M	Silicosis	<i>A. baumannii</i>	3	ETA	Col, GN, AK, TIG	Dead
9	58/F	COAP	<i>P. aeruginosa</i>	4	BAL	Col	Dead
10	48/F	Cystic fibrosis	<i>A. baumannii</i>	3	Blood	Col	Dead

BAL: Bronchoalveolar lavage fluid; Col: Colistin; GN: Gentamicin; AK: Amikacine; TIG: Tigecycline; AB: Antibiotics; IPF: Idiopathic pulmonary fibrosis; COPD: Chronic obstructive pulmonary disease.

**Table 3. Distribution of lung transplant donors by hospitals**

Hospital type	n	%
Training and Research Hospital	22	30
Private Hospital	20	27
Public Hospital	15	20
University Hospital	14	13

the Infectious Diseases Society of America (IDSA)/American Society of Health-System Pharmacists (ASHP)/Surgical Infection Society (SIS)/Society for Healthcare Epidemiology of America (SHEA) guidelines recommend a single dose of first-generation cephalosporin for prophylaxis.<sup>[4]</sup> Due to the frequent occurrence of Gram-negative and fungal infections in LTx recipients, many centers worldwide administer more extensive prophylaxis. A potential approach would be the use of the third-generation cephalosporin or cefepime plus vancomycin.

Ceftazidime is considered as the first-line treatment option for patients without a septic condition using a bacterial colonization-free graft; piperacillin-tazobactam, and cefepime are useful alternatives to ceftazidime; and levofloxacin can be administered in patients with beta-lactam allergy. Vancomycin is often used in combination with ceftazidime for Gram-positive bacteria. Regular follow-up visits performing bronchoscopy are recommended after transplantation.<sup>[6,7]</sup> In the presence of signs of complications in the postoperative clinical course, antibiotic prophylaxis should be continued. Treatment with antibiotics should be directed against isolated pathogens. Patients who receive grafts from donors infected with known pathogens should be treated with an appropriate antibiotic regimen for a reasonable period of time until at least two consecutive bronchoalveolar lavage cultures prove negative.<sup>[8]</sup>

In the current study, a broad-spectrum antimicrobial regimen of parenteral vancomycin, levofloxacin, and cefepime was administered to all LTx recipients, postoperatively. Antibiotics were continued for three to five days after transplantation while pending the results of perioperative bronchial cultures and preoperative respiratory cultures. All antimicrobials were discontinued, once aforementioned cultures proved sterile. Once positive cultures were discovered, however, antibiotic therapy was tailored to identified bacterial organism(s) and continued for a total of 10 to 14 days.<sup>[9]</sup>

Lung transplant donors are often brain-dead patients in the ICUs who are at a high risk for being colonized or even become infected with microorganisms during their ICU stay. Infections with resistant microorganisms are common, particularly during prolonged hospital or ICU stays, which increase the risk of donor-derived infections. The incidence of donor-derived bacterial infections varies from one study to another. Mularoni et al.<sup>[10]</sup> examined 170 donors in 10 hospitals in Italy and reported that 18 donor lungs (10.5%) were colonized or infected with carbapenem-resistant Gram-negative bacteria. Therefore, screening for colonization or infection taking account of pathogens in donor lungs is particularly important.

The incidence of donor-derived bacterial infection was 6.25% in a study of 80 patients by Bonde et al.<sup>[11]</sup> between 1998 and 2001, and was 6.8% by Tanaka et al.<sup>[12]</sup> in 175 LTx patients between 2006 and 2012, and Ruiz et al.<sup>[13]</sup> reported 12 of 202 (5.7%) patients, which was 14% higher in our study than in other studies.<sup>[14-16]</sup>

Whether pathogenic microorganisms in donor lungs affect the prognosis of LTx recipients still remains unclear. Bonde et al.<sup>[11]</sup> reported that, of 64 donors, 57 (89%) cultures of bronchial secretions of grew bacteria, which confirmed that colonization of pathogenic microorganisms in donor lungs was common. No significant relationship was reported between the culture results of bronchial secretions and pneumonia after LTx. Most symptomatic infections of recipients were not directly related to the presence of donor organisms. No correlation was reported between organisms identified in donor cultures and pathogenic organisms infecting recipients.<sup>[17]</sup>

A study by Avlonitis et al.<sup>[18]</sup> retrospectively analyzed the culture of lung alveolar lavage fluid in 115 LTx recipients, of whom 62 (54%) had negative and 53 (46%) positive cultures of pulmonary alveolar lavage fluid. The mean duration tracheal intubation and that of ICU stay were longer in the positive culture group. Bacterial colonization of lower airways of donors was attributable to the differences in the preservation methods, the diverse preservation solutions, antibiotic choices for prophylaxis, and culture protocols regarding surveillance for bacterial contamination developed in several studies. In LTx, Low et al.<sup>[7]</sup> reported that 97% of donors were infected or colonized and that the same organism was isolated in 43% of recipients, but of whom about 80% had no invasive pulmonary infection. It is important to isolate the agent from samples taken from donors, grafts, preservation solutions,

and recipients.<sup>[19]</sup> The regulation of antimicrobial therapy for the isolated agent is critical to reduce mortality. Inappropriate antibiotic choice during follow-up and postoperative treatment of transplant patients in the ICU is also an important risk for infection and colonization of carbapenem-resistant microorganisms or multi-resistant microorganisms.<sup>[20]</sup> In their study, Martin *et al.*<sup>[21]</sup> reported that donors who were followed could become infected with multidrug-resistant nosocomial bacteria within two days and transmit these bacteria to recipients.

In recent studies, the incidence infection with multi-antibiotic-resistant microorganisms has been increasing in donor-derived bacterial infections in LTx. In the study by Bunsow *et al.*,<sup>[22]</sup> 4.9% of LTx recipients were colonized and infected with resistant microorganisms of *Enterobacteriales*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*. The current study found that, of the infectious isolates, eight were resistant to multiple antibiotics. The administration of antibiotics to donors who are usually brain-dead patients admitted to the ICUs is considered to be associated with a risk for infections with resistant microorganisms.<sup>[23]</sup> Multidrug-resistant organisms (MDRO) are an emerging area of concern in transplantation. Transmissions of MDROs have been associated with poor recipient outcomes. While Disease Transmission Advisory Committee data did not uniformly include antimicrobial susceptibility information, it is notable that among 80 bacterial pathogens transmitted methicillin-resistant *Staphylococcus aureus*, VRE, *Acinetobacter* spp., *Burkholderia*, and *Pseudomonas* accounted for 36% of transmitted bacteria.<sup>[24]</sup>

Lung transplant recipients routinely receive perioperative antibiotic prophylaxis, but antibiotic regimens may vary widely depending on underlying lung disease, pre-transplant bacterial colonization, results of antibiotic sensitivity testing, and local protocols. Guidelines for antimicrobial prophylaxis in surgery recommend the use of cefazolin for heart and LTx, although the evidence is mostly based on cardiac procedures.<sup>[18]</sup> Cystic fibrosis, COPD and, less frequently, interstitial lung diseases may have bronchial colonization, possibly by hospital-acquired microorganisms with multidrug resistance.<sup>[21]</sup> Also, the donor may have a clinical infection such as ventilator-associated pneumonia.

Considering the results of donor lung tissue cultures in the choice of treatment for donor-derived bacterial infections, initiation of empirical therapy

may reduce the incidence of mortality associated with donor-derived bacterial infections in transplant recipients and treatment modification. The incidence of donor-derived infections is still high. Accurate screening of donor-derived pathogenic or colonizing bacteria is crucial to reduce the recipient risk of infection.<sup>[24]</sup>

Our study has some limitations, including those inherent to a single-center and retrospective study.

In conclusion, the incidence of donor-derived bacterial infection in lung transplant recipients was higher than in previous years at our center, possibly due to the donors' prolonged hospital or intensive care unit stay and prior colonization or infection of the donor with resistant infections. Therefore, the sensitivity of donor cultures may be useful to establish treatment protocols once post-transplant infections while pending the cultures results.

**Ethics Committee Approval:** The study protocol was approved by the Kartal Koşuyolu High Speciality Educational and Research Hospital Ethics Committee (date: 25.9.2018, no: 2018.6/9-115). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Idea/concept: S.D.K.; Design: S.D.K.; Control/supervision: K.K.; Data collection and/or processing: S.D.K.; Analysis and/or interpretation: K.K., S.D.K., E.T.; Literature review: K.K., S.D.K., E.T.; Writing the article: K.K., S.D.K., E.T.; Critical review: K.K., S.D.K., E.T.; References and fundings: K.K., S.D.K., E.T.

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