Epidemiology and Clinical and Radiographic Characteristics of Pneumonia in Kidney Transplant Recipients; 24-Year Experience

Böbrek Nakil Hastalarında Gelişen Pnömonilerin Epidemiyolojisi, Klinik ve Radyografik Karakteristikleri; 24 Yıllık Tecrübe

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ABSTRACT

OBJECTIVE: Pneumonia increases morbidity and mortality in kidney transplant (KT) recipients. This study aimed to investigate characteristics of pneumonias in KT recipients by focusing on clinical and radiographic findings and diagnostic methods over a long study period.

MATERIAL and METHODS: The medical records of kidney transplant recipients who had a diagnosis of pneumonia from 1988 to 2011 were reviewed retrospectively.

RESULTS: Among 406 consecutive KT recipients, 20% had pneumonia during the study period and total 111 episodes of pneumonia developed in these patients. Fifty-six percent of the pneumonias were community acquired and 44% nosocomial. Bacterial infections were the most common cause (20%) and 13 (12%) of the episodes were polymicrobial. Antibiotic usage in the last 3 months was significantly more common in fungal pneumonia episodes than others. Bronchoscopy had the highest final overall diagnostic yield.

CONCLUSION: Community-acquired pneumonia was more common, but it showed a more benign clinical course. Bacterial pneumonia was the most common cause, but polymicrobial infection was present in a significant number of KT recipients. Fungi can invade KT recipients, in particular, patients in the interval of 1-6 month after transplantation and patients who have used antibiotics in the last 3 months.

KEY WORDS: Pneumonia, Kidney transplantation, Radiography, Physical examination, Nosocomial

ÖZ

AMAÇ: Pnömoni böbrek nakil hastalarında morbidite ve mortaliteyi artırır. Çalışmada böbrek nakil hastalarında uzun bir zaman diliminde klinik ve radyografik bulgular ve tanısal yöntemlere odaklanarak pnömonilerin özellikleri incelendi.

GEREÇ ve YÖNTEMLER: Retrospektif olarak 1988 ile 2011 yılları arasında pnömoni tanısı almış böbrek nakil hastalarının bilgileri incelendi.

BULGULAR: Çalışma süresi içerisinde böbrek nakli yapılmış 406 hastanın %20'sinde pnömoni gelişti. Toplam pnömoni atak sayısı 111 idi. Pnömoni ataklarının %56'sı toplum, %44'ü nazokomial kökenli idi. Bakteriyel enfeksiyonlar en sık nedendi (%20) ve atakların 13'ü (%12) polimikrobiyaldi. Son 3 ay içinde antibiyotik kullanımı fungal pnömonilerde daha sıktı. Bronkoskopi en yüksek tanı koydurucu yöntemdi.

SONUÇ: Böbrek nakli hastalarında toplum kökenli pnömoniler daha sıktır ve daha iyi bir seyre sahiptir. Bakteriyel pnömoniler en sık neden olmasına rağmen polimikrobiyal enfeksiyonlarda oldukça sıktır. Fungal pnömoniler özellikle nakilden sonraki 1-6 aylık dönemde sıktır ve son 3 ay içinde antibiyotik kullanan hastalarda daha sık görülür.

ANAHTAR SÖZCÜKLER: Pnömoni, Böbrek nakli, Radyografi, Fizik muayene, Nazokomiyal

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INTRODUCTION

It is more difficult to recognize infection in immunosuppressed patients such as kidney transplant (KT) recipients than it is in persons with normal immune function, since signs and symptoms of infection are often diminished (1). An increased incidence and spectrum of opportunistic infections is observed due to the growing population of immunosuppressed patients with prolonged survival (2). In our cohort, the incidence of respiratory tract infections was 20%, and mortality rate was 25% in all pneumonia episodes identified (3). The prediction of possible pathogen and early diagnosis of lower respiratory tract infection in kidney transplant recipients are essential for good clinical outcomes and to minimize nonessential drug therapy that has toxic effects and interactions with immunosuppressive agents (1). Invasive diagnostic procedures are often required for accurate and timely diagnosis.

Many studies of pneumonia in KT recipients have been carried out to analyze risk factors and mortality. Less frequent studies have described physical examination findings, radiographic manifestations and diagnostic methods and most studies did not have a sufficient study period for detailed analysis. This retrospective study aimed to investigate characteristics of pneumonias in kidney transplant recipients by focusing on physical examination and radiographic findings and diagnostic methods for a long study period.

MATERIAL and METHODS

The medical records of kidney transplant recipients who had a diagnosis of pneumonia from December 1988 to April 2011 (24 years) at the transplant unit of a university hospital were reviewed retrospectively. Data for the study were obtained from our transplant database and review of electronic and paper-based medical records. Patient's demographics, type of transplantation, primary diagnoses, immunosuppressant therapy, laboratory and radiologic findings were all recorded. The patients were evaluated in detail regarding their history of chronic pulmonary disease, tuberculosis, smoking and other risk factors such as diabetes (pre and post transplant).

The admission history and physical examination results were reviewed for the presence or absence of the following symptoms: fever, cough, hemoptysis, chills or rigors, headache, dyspnea, chest pain, nausea, vomiting, anorexia, and confusion. In cases of nosocomial acquisition, the progress notes of the week preceding the diagnosis of pneumonia were examined. Daily progress notes were reviewed for the presence of complications and/or concurrent infections, daily maximum temperature elevations, surgical procedures performed, and the need for intubation during hospitalization. All reports of radiographs and computerized tomography (CT) studies of the chest were reviewed for the location and type of pneumonic infiltrate and the presence of pleural effusion and/or pulmonary cavitation.

Subjects were included if they developed radiological (X-ray chest and/or CT chest) features suggestive of pneumonia, with one or more of the following respiratory manifestations: cough with or without expectoration, dyspnea, pleuritic chest pain and reduced partial pressure of oxygen in arterial blood. Presence of fever was not mandatory for defining pneumonia. The diagnostic strategies implemented at the time of suspicion of pneumonia included noninvasive tests (high-resolution computed tomography, blood cultures, sputum examination, urine and serum antigens, polymerase chain reaction assay for cytomegalovirus, and Aspergillus antigenemia) with or without fiberoptic bronchoscopy and bronchoalveolar lavage. Gram and Ziehl-Neelsen stained respiratory samples were cultured for bacterial pathogens, fungi, and mycobacteria. Serologic tests were performed for CMV, Chlamydia, Mycoplasma, and Legionella. The diagnosis was based on the presence of radiologic evidence of a pulmonary infiltrate and a compatible clinical illness in the absence of signs of congestive heart failure, pulmonary emboli or a neoplasm. If the bronchoscopy findings altered medical management and produced improvement in pneumonia, the procedure was considered diagnostic. We defined nosocomial pneumonia as pneumonia acquired at least 48 hours after admission to hospital (4). The response to therapy was monitored on the basis of resolution of symptoms and signs, improvement in arterial blood gases values and radiological resolution. The severity of pneumonia was assessed with CURB-65 criteria for community-acquired pneumonia; based on the modified British Thoracic Society assessment tool, the CURB severity score (range, 0-4 points) was calculated as the sum of points given for each feature present (1 point for each feature): confusion, urea > 7 mmol/L, respiratory rate > 30 breaths/min, and low blood pressure (diastolic < 60 mm Hg or systolic < 90 mm Hg) (5).

All patients received initial immunosuppressive therapy with prednisolone, antimetabolites (mycophenolate mofetil-MMF or azathioprine-AZA) combined with calcineurin inhibitors (CNI; CsA or tacrolimus-Tac) or mTOR inhibitors (sirolimus-SRL or everolimus-EVL) with interleukin-2 receptor antagonists (IL-2ra) or antithymocyte globulin (ATG) induction. Acute rejection was treated with methyl-prednisolone (1 g/day for 3 days, intravenously) as the first line treatment. ATG was given for steroid-resistant rejection. During the pneumonia episode, decision of reduction of immunosuppressive therapy was individualized according to the patient's clinical status. When there was poor response to treatment or the course of pneumonia was serious and progressive, AZA or MMF were withdrawn first, followed by CNIs too if required.

Statistical Analysis

All calculations used the SPSS statistical package (version 15.0; SPSS, Chicago, IL, USA). Data were presented by using absolute and percentage frequencies, means, and standard deviations. Categorical variables were compared using the c2 test or Fisher exact test when appropriate. The normality and the homogeneity of the data were evaluated with the Shapiro-Wilk test and Levene test, respectively. Comparisons between groups for continuous variables were performed using the Student

t test (normal distribution) or the Mann-Whitney U test (non-normal distribution). Continuous Scale values of all etiologic groups were compared using Kruskal-Wallis analysis (for non-parametric data) or ANOVA was used to compare the difference among these patient groups. $P < 0.05$ was considered statistically significant.

RESULTS

We reviewed the clinical records of 406 consecutive kidney transplant recipients, of whom 248 (61%) was male. Approximately 37.4% (152) of the cohort had received a deceased donor kidney. The mean age of the patients was 34.5 ± 11.5 years. The majority of the cohort had been on hemodialysis (n = 260, 75.1%). Mean dialysis duration was 4.7 ± 3.8 years. The most common causes leading to renal failure were hypertensive nephropathy (56 cases, 16.8%) and glomerulonephritis (39 cases, 11.7%). In the majority of patients, the primary cause of renal failure was unknown as most of these patients had presented for the first time in advanced renal failure. Diabetes mellitus was present in 25 patients (6.3%). The number of recipients with positive anti HCV, HBsAg and CMV Ig M test before the kidney transplantation were 28 (9.3%), 7 (2.3%), and 18 (11.3%), respectively. Forty-three patients (18.5%) experienced acute rejection, and 21 patients (8.3%) chronic rejection. Total mortality rate from any cause was 17% (n = 69).

Pneumonia Incidence and Series Description

According to our patient records, 82 of 406 kidney transplant recipients (20%) had pneumonia during the study period (24 years). A total of 111 episodes of pneumonia developed throughout the study period in these 82 patients. The mean age ± SD of the patients was 37.6 ± 12.29 years; 72% (n = 59) were male. Fourteen patients had two episodes, 6 patients had three episodes and 1 patient had four episodes of pneumonia. The mean interval from transplantation to the onset of pneumonia was 22.2 ± 32.7 months. Eleven percent of the 111 pneumonia episodes were developed within 1 month of transplantation; 35%, 1-6 months after transplantation; and 54%, >6 months after transplantation. Fifty-six percent of the pneumonias were community acquired and 44% nosocomial. Twenty-eight patients (25.2%) died due to pneumonia. Intensive care follow-up was required in 30 pneumonia episodes and 28 of them resulted in mortality. Other characteristics of the episodes of pneumonia are shown in Table I. The distribution of episodes by year is shown in Figure 1.

Table I: Characteristics of the episodes of pneumonia.

	Pneumonia Episodes (n = 111)
Etiology of pneumonia, n(%)	
Bacterial	22 (20)
Fungal	13 (12)
Viral	7 (6)
Unknown	56 (50.4)
Polymicrobial	13 (12)
Comorbidities and risk factors, n(%)	
History of tuberculosis	5 (6.1)
Obesity	6 (7.3)
Diabetes mellitus	10 (12.2)
Hypertension	42 (51.2)
Cardiac disease	12 (14.6)
Bronchiectasis	2 (2.4)
Asthma	1 (1.2)
COPD	1 (1.2)
Smoking, n(%)	26 (31.7)
Immunosuppressive regimen, n(%)	
MMF/Tac/P	26 (31.7)
MMF/CyA/P	23 (28)
AZA/CyA/P	20 (24.4)
EVL/MMF/P	3 (3.7)
SRL/MMF/P	1 (1.2)
Delayed graft function history, n(%)	27 (32.9)
Post-transplant dialysis requirement, n(%)	24 (29.3)
Acute rejection history, n(%)	24 (29.3)
Chronic rejection history, n(%)	11 (13.4)

COPD: Chronic obstructive pulmonary disease, **EVL:** Everolimus **MMF:** Mycophenolate mofetil, **P:** Prednisolone, **Tac:** Tacrolimus, **CyA:** Cyclosporine, **AZA:** Azathioprine, **SRL:** Sirolimus.

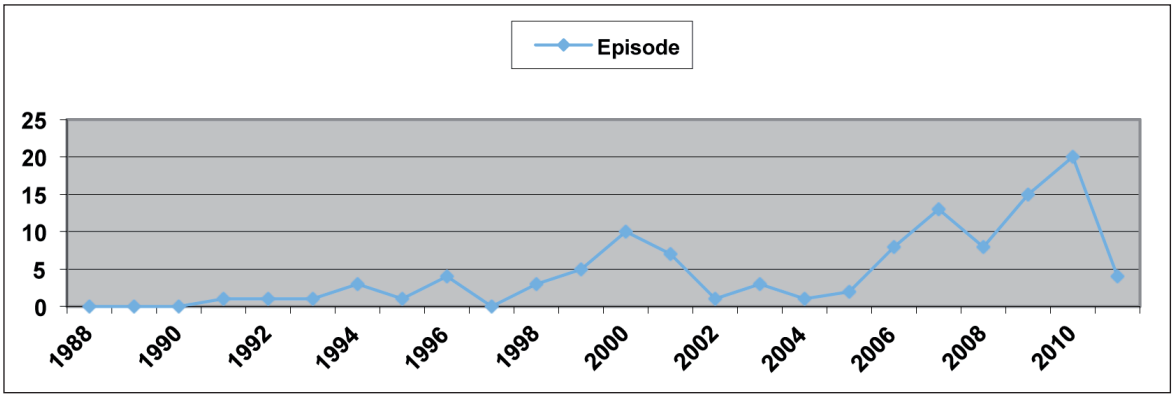

Figure 1: *The distribution of episodes by year.*

We determined two peak periods; one of them between 1999 and 2001, the other and bigger peak between 2006 and 2011. The etiology of the pneumonia episodes was similar in the two peak periods but all viral and *Pneumocystis jiroveci* pneumonia cases occurred between 2006 and 2011.

Etiology

The etiology was established for 55 episodes (49.5%) of pneumonia; 13 (12%) of the episodes were polymicrobial. Bacterial infections were the most common cause (20%), especially *Haemophilus influenza, Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. Among 50.4% (n = 56), there was no positive microbiologic isolation. Of the total number of episodes, fungal infections, especially *Aspergillus fumigatus,* represented 12% and viral 6%. Nine patients had positive mycobacterial tuberculosis culture findings from the lower respiratory specimen. Aspergillus spp. were isolated in 18 episodes, nocardia 1 episode, and *Pneumocystis jiroveci* 3 episodes. Antibiotic usage in the last 3 months was more common in fungal pneumonia episodes than viral or bacterial pneumonia episodes (positive in 22 fungal episodes among total 25 fungal episodes) (p = 0.006).

Diagnostic Procedures and Radiographic Manifestations

Various diagnostic procedures were used in patients who had symptoms of pneumonia and were often combined with each other. Diagnosis was achieved in 35 episodes by only physical examination and chest radiography. When this method was nondiagnostic or multiple, bilateral, or diffuse pulmonary infiltrates were determined, computerized chest tomography (n = 53), fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) (n = 12) and lung biopsy (n = 2) were performed. Physical examination findings compared by etiologies of 111 episodes of pneumonia are summarized in Table II. Bronchoscopy was the diagnostic procedure most commonly used for obtaining respiratory samples and was performed in 23 episodes, giving a final overall diagnostic yield of 12 patients (52.2%). The detailed results of the bronchoalveolar lavage specimen cultures are shown in Figure 2. Twenty-six patients showed an adequate gram stain with positive lower respiratory tracts culture findings for definitive diagnosis. Simple x-rays were obtained in all episodes of pneumonia and 97 of them had pathologic findings. Radiographic findings compared by etiologies of 111 episodes of

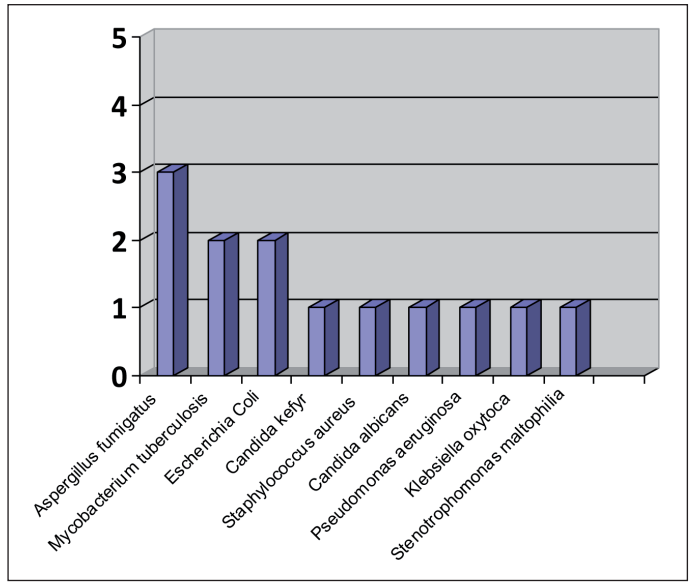

Figure 2: *Results of the bronchoalveolar lavage cultures.*

Table II: Physical examination findings compared by etiology for the 111 episodes of pneumonia in kidney transplant recipients.

Finding	Total (n=111)	Bacterial (n=22)	Fungal (n=13)	Viral (n = 7)	Unknown etiology (n = 56)	Polimicrobial (n = 13)	p=
Early inspiratory crackles (rales), n(%)	47(42)	8(36)	5(38)	2(28)	29(52)	3(23)	0.633
Coarse crackles, n(%)	30(27)	4(18)	4(31)	2(28)	13(23)	7(54)	0.075
Rhonchi, n(%)	19(17)	3(14)	0	2(28)	14(25)	0	-
Decreased breath sounds, n(%)	11(10)	3(14)	1(8)	0	5(9)	2(15)	-
Pleural friction rub, n(%)	1(1)	0	0	0	1(2)	0	-
Systolic blood pressure, mmHg	130 ± 23	124 ± 23	123 ± 17	121 ± 9	133 ± 27	132 ± 17	0.121
Diastolic blood pressure, mmHg	78.5 ± 13	76.5 ± 14	76 ± 10	76 ± 5	79 ± 14	85 ± 12	0.168
Pulse, beat/minute	96 ± 15	98 ± 14	91 ± 7	88 ± 7	95.5 ± 16	103 ± 18	0.201
Temperature, °C	38 ± 0.9	38 ± 1	38 ± 0.7	37 ± 0.9	38 ± 0.8	38 ± 0.8	0.110
CURB-65 score	1.2 ± 0.7	1.1 ± 0.5	1 ± 0	1.2 ± 0.5	1.2 ± 0.7	1.6 ± 0.9	0.683

CURB_65: the CURB severity score (range, 0-4 points) was calculated as the sum of points given for each feature present (1 point given for each feature): confusion, urea > 7 mmol/L, respiratory rate > 30 breaths/min, and low blood pressure (diastolic < 60 mm Hg or systolic < 90 mm Hg)

pneumonia are shown in Table III. Only 4 episodes had normal chest radiography but abnormal computerized chest tomography findings. Alveolar and mix infiltrates were the most common chest radiographic appearance of pneumonia and the right lung involved in 44 episodes (39.6%), left lung in 21 episodes (18.9%), and bilateral in 32 (28.8%). Bilateral involvement of the lung was significantly lower in fungal infections (p = 0.006). The lower zone of the lung was the most common site of pneumonia (in 57 episodes, 51.3%). Pleural effusion was seen in 16 episodes (14.4%), nodular lesions in 8 episodes (7.2%), cavitary lesions in 10 episodes (9%) and reticulonodulary appearence in 2 episodes (1.8%). Cavitary lesions were significantly more common in fungal and polymicrobial infections (p < 0.001 and p < 0.001; respectively).

Clinical Manifestations and Complications

The most common presenting symptom was fever with or followed by cough (n = 81) or sputum (n = 51). There were 24 instances of shortness of breath, 8 hemoptysis, 5 chest pain and 4 pleuritic chest pain. The main clinical characteristics and outcome compared by etiology of the 111 episodes of pneumonia are shown in Table IV. At least one complication developed in 40 (36%) pneumonia episodes during treatment of pneumonia. Hematologic complications developed (leukopenia, trombocytopenia or pancytopenia) in 22 episodes, renal impairment in 14 episodes and hepatotoxicity in 7 episodes. Among 111 pneumonia episodes, leukopenia was present in 11 episodes and 6 of these episodes were fungal (p = 0.015). Although pneumonias presented as an isolated process in most episodes, thirty-eight episodes (34.2%) had an extrapulmonary infection during pneumonia and the most common sites for secondary or concurrent infection were the urinary tract (n = 11). Extrapulmonary infections were more common in viral and polymicrobial episodes (p = 0.045 and p = 0.001; respectively) and were less common in episodes with unknown etiology (p = 0.001) Antibiotic usage in the last 3 months was more common in fungal episodes (p = 0.006).

Comparison of Community and Nosocomial Pneumonia

Nosocomial pneumonias accounted for 71.4% of pneumonia episodes resulting in mortality and this difference was statistically significant (p= 0.001). Pneumonia occurrence time after transplantation was significantly earlier in nosocomial pneumonia than in community acquired ones (15 and 27.9 month; respectively). There was no difference in immunosuppressive drugs and dosage between groups, but only mean P dose was higher in nosocomial pneumonia (52.7 mg and 15.7 mg; p < 0.001; respectively). Nosocomial pneumonia episodes had higher procalcitonin, urea, LDH values and lower hemoglobin, albumin values, but there were no significant differences for creatinine, sedimentation, C-reactive protein, or leukocytes. Table V summarizes the differences between community acquired and nosocomial pneumonia.

Table III: Radiographic findings compared by etiologies of 111 episodes of pneumonia in kidney transplant recipients.

Finding	Total (n = 111)	Bacterial (n = 22)	Fungal (n = 13)	Viral (n = 7)	Unknown etiology (n = 56)	Polimicrobial (n = 13)	p=
Alveolar infiltrate, n(%)	97(87)	17(77)	12(92)	5(71)	50(89)	13(100)	0.191
Affected lung, n(%)							0.210
Right	44(40)	8(36)	5(38)	3(43)	22(39)	6(46)	
Left	21(19)	3(14)	6(46)	1(14)	7(12.5)	4(31)	
Bilateral	32(29)	6(27)	1(8)[a]	1(14)	21(37.5)	3(23)	
Infiltrative Zone, n(%)							-
Lower	39(35)	6(27)	3(23)	2(29)	24(43)	4(31)	
Middle	11(10)	2(9)	4(31)	0	4(7)	1(8)	
Upper	13(12)	3(14)	2(15)	1(14)	4(7)	3(23)	
Multilobar	34(31)	6(27)	3(23)	2(29)	18(32)	5(38)	0.954
Interstitial infiltrate, n(%)	2(2)	2(9)	0	0	0	0	-
Nodules, n(%)	8(7)	1(4.5)	3(23)	1(14)	2(4)	1(8)	-
Pleural effusion, n(%)	16(14)	1(4.5)	1(8)	1(14)	10(18)	3(23)	-
Cavitation, n(%)	10(9)	0	4(31)[b]	0	1(2)	5(38)[c]	-

[a]: p = 0.006, bilateral affected lung was significantly lower in fungal infections.

[b,c]: cavitation was significantly more common in fungal and polymicrobial infections (p < 0.001 and p < 0.001; respectively).

DISCUSSION

Pneumonia continues to be one of the most frequent infectious complications in kidney transplant patients. In this study, we provided a detailed analysis about this important issue and our study has some advantages to other studies conducted to date in the literature. Our study covers for a long period of time and the number of attacks was higher than other similar studies. It was important to see etiological differences. Furthermore, only kidney transplant recipients were investigated in the present study, whereas most similar studies are on solid organ transplant recipients. Because different organ transplants involve different immunosuppressive protocols, we provide highly specific information on this topic. To our knowledge, this is the biggest survey and epidemiologic analysis of pneumonia in KT recipients from TURKEY. In this retrospective analysis of KT recipients, pneumonia cases were investigated in all patients for 24 years.

A 10% - 13% incidence of pneumonia among the renal allograft recipients was reported in the 1980s (6,7). However, in another study involving 610 patients (8), the incidence was 8.8% and in studies from the asian region, the incidence was 12% - 18% in the 1990s (9,10). Total pneumonia incidence was 20% in our study. Our study shows an incidence of pneumonia higher than previously reported. When we examine the distribution of attacks according to year, there has been a dramatic increase in the incidence of pneumonia after 2006. Besides our long study period, which may be the major factor, lack of proper hygiene, poor socioeconomic status and the endemic nature of certain infections contribute to this high incidence of post transplant infections.

Table IV: The main clinical characteristics and outcome compared by etiologies of 111 episodes of pneumonia in kidney transplant recipients.

Finding	Total (n = 111)	Bacterial (n = 22)	Fungal (n = 13)	Viral (n = 7)	Unknown etiology (n = 56)	Polimicrobial (n = 13)	p=
Death, n(%)	28(25)	6(27)	2(15)	1(14)	13(23)	6(46)	0.373
Mechanical ventilation, n(%)	30(27)	7(32)	3(23)	1(14)	13(23)	6(46)	0.454
Immunosuppressive medications, n(%)							
Cyclosporine	48(43)	11(50)	5(38)	3(43)	24(43)	5(39)	0.974
Mycophenolate mofetil	69(62)	12(55)	9(69)	6(86)	33(59)	9(69)	0.564
Tacrolimus	52(47)	7(32)	7(54)	4(57)	27(48)	7(54)	0.595
Sirolimus	4(4)	1(5)	1(7.7)	0	2(3.6)	0	-
Azathioprine	17(15)	4(18)	2(15)	0	9(16)	2(15)	-
Everolimus	2(2)	0	0	0	2(3.6)	0	-
Dose of prednisolone, mg	32 ± 95	67 ± 209	21 ± 14	16 ± 9	25 ± 26	25 ± 10	0.443
Increase in immunosuppression, n(%)	54(49)	10(45)	8(62)	4(57)	25(45)	7(54)	0.805
Antibiotic usage in the last 3 months, n(%)	72(65)	14(64)	12(92)[a]	7(100)	29(52)[b]	10(77)	0.009
History of acute rejection, n(%)	31(28)	5(23)	3(23)	2(29)	18(32)	3(23)	0.917
Complications occurrence, n(%)	40(36)	7(32)	5(38)	6(86)	12(21)	10(77)	0.197
Extrapulmonary infection, n(%)	38(34)	8(36)	6(46)	5(71)[c]	10(18)[d]	9(69)[e]	0.001
Age at the time of pneumonia, year	40 ± 12	38 ± 13	42 ± 15	35 ± 6	42 ± 12	36 ± 9	0.278
Pneumonia occurring time after KT, month	22 ± 33	14 ± 23	28 ± 44	7 ± 10	29 ± 36	10 ± 13	0.114
Duration of hospitalization, day	26 ± 21	29 ± 20	41 ± 24	29 ± 13	15 ± 11[f]	48 ± 24	<0.001

[a]: p = 0.006, Antibiotic usage in the last 3 months was significantly higher in fungal infections.

[b]: p = 0.002, Antibiotic usage in the last 3 months was significantly lower in unknown etiology.

[c,e]: Extrapulmonary infections were significantly higher in viral and polymicrobial infections (p = 0.045 and p = 0.001; respectively)

[d]: p = 0.001, Extrapulmonary infections were significantly lower in unknown etiology

[f]: Duration of hospitalization was significantly lower in unknown etiology.

The etiology of pneumonia in kidney transplant recipients is diverse. As seen in previous studies, bacterial pneumonia was the most frequent etiology in our kidney transplant recipients population and was microbiologically diagnosed in 22 episodes (20%) (11,12). Similar to other studies, the most frequent bacterial etiologies of pneumonia reported in KT patients were *Haemophilus influenza and Pseudomonas aeruginosa* (11,13). Gram-negative bacteria are the microorganisms that most frequently cause pneumonia after KT; they accounted for more than 50% of the isolates in this study, like Chang et al.'s study (11). Some of pneumonias after KT are polymicrobial, as were 12% (n = 13) of our cases and 11% - 23.9% of the cases in other studies (11,14) and fungi are the most common copathogen, occurring in 68% of our polymicrobial cases and in 36% of cases in other study (14). This association is possibly related to our higher incidence of fungal infections. Viral infections are less common copathogens. Table VI shows the spectrum of pneumonia in different studies.

From our data it is apparent that patients who have no cause established for the pneumonia responded promptly to empiric antibiotic treatment and usually had a short hospital stay. Antibiotic usage in the last 3 months was significantly lower in these patients.

Fungal infections, especially *Aspergillus*, have high mortality rates in immunocompromised patients (15) and in KT recipients due to the use of immunosuppressive agents such as corticosteroids (16). *Aspergillus* species were the second most common cause of pneumonia in our study (16% of the episodes); the incidence of aspergillus pneumonia was higher than that (5%) described in other European studies (8). The most important risk factors for fungal infection in other studies were steroids, acute rejection episodes associated with high steroid dosages, broad spectrum antibiotic treatment and long intensive care unit stays (17). In our study, fungal pneumonia was significantly associated with a higher frequency of antibiotic usage in the last 3 months than were pneumonias caused by other agents. This situation and environmental factors, the main risk factors for the development of pulmonary aspergillosis, may have contributed to higher fungal pneumonia episodes. In our study, we believe that reducing the unnecessary use of antibiotics and early pathogen identification are critical steps to limit aspergillosis.

Table V: Differences between Community and Nosocomial Pneumonia.

	Community (n = 62)	**Nosocomial (n = 49)**	**p=**
Increase in immunosuppression, n(%)	17 (27.4)	37 (75.5)	<0.001
Antibiotic usage in the last 3 months, n(%)	33 (53.2)	39 (79.6)	0.004
Type of pneumonia, n(%)			
Bacterial	16 (25.8)	18 (36.7)	NS
Fungal	7 (11.2)	18 (36.7)	0.002
Viral	6 (9.7)	4 (8.2)	NS
Diabetes mellitus, n(%)	3 (4.8)	11 (22.4)	0.006
Oxygen demand, n(%)	8 (12.9)	27 (55.1)	<0.001
Culture growth, n(%)	23 (37.1)	30 (61.2)	0.012
Complication during treatment of pneumonia, n(%)	19 (30.6)	21 (42.9)	NS
Extrapulmonary infection, n(%)	14 (22.6)	24 (49.0)	0.004
Intensive care unit admission, n(%)	8 (12.9)	22 (44.9)	<0.001
Duration of hospitalization, day	20.8 ± 16.1	31.5 ± 23.4	0.01
Laboratory findings[1]			
Procalcitonin, ng/mL	1.88 ± 2.58	9.1 ± 16.5	0.018
Urea, mg/dL	80.1 ± 53.4	116 ± 60	<0.001
Hemoglobin, g/dL	11.4 ± 2.6	9.5 ± 1.9	<0.001
Albumin, g/dL	3.2 ± 0.7	2.9 ± 0.8	<0.005
LDH, U/L	335.5 ± 141.3	418.1 ± 219.4	<0.019

[1]: Only significantly different findings were demonstrated. **NS:** Not significant, **LDH:** Lactate dehydrogenase

P. carini pneumonia incidence was 2.7% (3 cases), similar to the 1.6% reported in another European study (6). Prophylactic co-trimoxazole is effective and reduces the incidence of *P. carini pneumonia* (18). Two of the 3 cases had received a kidney transplant 2 and 8 years before; therefore, they were not receiving prophylaxis with co-trimoxazole (as co-trimoxazole prophylaxis is administered only in the first 6 to 9 months after transplantation at our center). There were no any acute rejection episodes or increase in immunosuppression in these patients' history. Only one patient had simultaneous CMV pneumonia and this coexistence may have contributed to the development of *P. carini pneumonia*. None of them died. Pulmonary tuberculosis is an endemic disease throughout Asia. The incidence of pulmonary tuberculosis was 8.1% (9 cases), higher than the rate of 1.6% reported in Europe and lower than the rate of 37% reported in India (8,9). Other opportunistic microorganisms are far less common. The incidence of nocardia pneumonia was 0.9% (1 case).

The timetable of infection in the organ transplant recipient, described by Fishman and Rubin for KT recipients, has been useful for the diagnosis (19). In this study, like Fishman and Rubin, we classified the pneumonia episodes for occurrence time after KT. Invasive pulmonary aspergillosis was significantly more frequent in the interval of 1-6 months after transplantation. This finding was consistent with the literature but there was no significant difference for other opportunistic microorganisms regarding pneumonia occurrence time.

No clear relationship between immunosuppressive drugs and type of infection was detected, as in previous studies by Hill et al. and Huertas et al. (20,21). Likewise, there was no significant difference in mean daily prednisone dosage received by patients with pneumonia and others in our study.

Different radiologic techniques were used for establishing diagnosis. CT is more sensitive than simple x-rays for the diagnosis of acute pulmonary complications in immunosupressed patients. CT improved the information obtained from simple x-rays in four cases, who had normal simple x-ray findings. In our study, 50% of patients had undetermined causes of pneumonia, similar to the results of a study by Hoyo et al. (47%), but higher than those of the studies by Jha et al. (14%), Luo et al. (17.5%) and Chang et al. (22.8%) (8-11). For this reason, quick diagnostic procedures that guide the antimicrobial treatment are necessary. BAL is the most important diagnostic procedure; the sensitivity of BAL was 52.2% in our study and 66.6% in another study (22). Although BAL has lower diagnostic success in our study than similar studies in the literature, it was found to be one of the best diagnostic methods. Despite the controversy about the routine use of bronchoscopy, many studies have demonstrated the safety and suitability of the use of bronchoscopy in appropriate patients (11,23,24). Its early use has been recommended especially, in severe nosocomial pneumonia cases (22). Examination of sputum and blood cultures should form part of the initial diagnostic study of pneumonia after KT, taking into account its limited sensitivity. Open lung biopsy is considered the "gold standard" for evaluation of lung infiltrates in the immunocompromised host.

Table VI: Spectrum of pneumonia in different studies[1].

	Present study (Turkey)	**Hoyo et al. (Spain) (Ref No = 8)**	**Jha R et al. (India) (Ref No = 10)**	**Luo W (China) (Ref No = 9)**	**Munda et al. (USA) (Ref No = 14)**	**Cervera et al. (Spain) (Ref No = 22)**	**Sousa et al. (Brasil) (Ref No = 25)**
Episodes	111	60	27	57	46	40	99
Bacterial, n(%)	33(29.7)	26(43)	19(70.3)	38(71.9)	34(73.9)	17(42.5)	unknown
Fungal, n(%)	25(22.5)	4(7)	8(29.6)	6(10.5)	8(17.3)	5(12.5)	unknown
Viral, n(%)	10(9)	2(3)	0 (0)	0 (0)	7(15.2)	1(2.5)	unknown
Undetermined etiology, n(%)	56(50.4)	28(47)	4(14)	10(17.5)	0(0)	17(42.5)	59(59)
Specific etiology							
Tuberculosis, n(%)	9(8.1)	1(1.6)	10(37)	3(5.2)	2(4.3)	2(5)	unknown
Pneumocystis jiroveci, n(%)	3(2.7)	1(1.6)	2(7.4)	unknown	6(13)	0(0)	2(2)
Aspergillosis, n(%)	18(16.2)	3(5)	2(7.4)	unknown	1(2.1)	5(12.5)	unknown
Nocardia, n(%)	1(0.9)	0(0)	2(7.4)	unknown	1(2.1)	0(0)	unknown

[1]: The total number for the etiology including those that caused polymicrobial infection are given.

Pneumonia in KT patients follows 2 patterns of appearance. Although nosocomial infections in the posttransplantation period have high mortality rates, community-acquired pneumonia follows a benign course. Furthermore, some significant findings were detected for nosocomial pneumonia in our study. Increase in immunosuppression, antibiotic usage in the last 3 months and diabetes mellitus were significantly associated with nosocomial pneumonia and it had a worse prognosis than community-acquired pneumonia. Therefore, methods of early diagnosis for hospitalized KT recipients are necessary to prevent nosocomial pneumonia, and early diagnosis of pneumonia in KT recipients reduces mortality (6).

In conclusion, two well-defined patterns of pneumonia were identified in renal transplant patients. Community-acquired pneumonia was more common, but it showed a more benign clinical course. Nosocomial lung infections have a high morbidity, with more patients requiring invasive mechanical ventilation in intensive care units, and, consequently, a higher mortality. Bacterial pneumonia was the most common cause, but polymicrobial infection was present in a significant number of KT recipients with pneumonia. The search for the etiological agent should not stop with the isolation of one organism only, especially if the response to therapy against a single etiological agent is partial and/or delayed. We should keep in mind that fungi can invade KT recipients, in particular, patients in the period of 1-6 months after transplantation and patients who have used antibiotics in the last 3 months. Further studies with larger sample size and longer observation are needed to evaluate the role of immunosuppressive and prophylactic/therapeutic antimicrobial agents on the pattern of pneumonias.

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