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Evaluation of infections in patients with kidney and liver transplantation

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ABSTRACT

Objectives: Infection is a frequent complication of organ transplantation and is associated with significant morbidity and mortality.

Methods: Patients who had liver and kidney transplants between 2011 and 2022, who were hospitalized in our hospital, and who were consulted for infectious diseases were retrospectively analyzed from hospital records.

Results: Of the patients included in the study, 9 (28%) were female, 23 (72%) were male, and the mean age was 33.7 ± 11.3 years. Patients had congestive heart failure (87.2%, n = 28), hypertension (43.7%, n = 14), and chronic obstructive pulmonary disease (21.8%, n = 7). Twenty (62.5%) kidney transplant recipients and 12 (37.5%) liver transplant recipients were seen within ten years. The most common infections were urinary tract infection in 8 (25%) patients and pneumonia in 11 (34.3%). The other infections were gastrointestinal infections such as diarrhoea, bloodstream infections and COVID-19 and Cytomegalovirus. Culture-isolated organisms in 20 (62.5%) of the 32 patients admitted with infections. The microbiological data were notable for some unusual and opportunistic pathogens, including one case of acute cytomegalovirus viremia. Severe sepsis had been seen in six (18.75%) out of 32 patients with documented infections.

Conclusions: Infection prevention has become a cornerstone of modern transplantation medicine due to the significant incidence of post-transplant infectious complications resulting from improved immunosuppressive therapies and surgical procedures.

Keywords: Liver transplantation, renal transplantation, infectious disease, post-transplant infections

For patients with failing organs such as kidneys, liver, heart, lung, and pancreas, solid organ transplantation (SOT) is the treatment of choice worldwide. According to the data of the Ministry of Health in our country, 17,406 liver transplants and 42,277 kidney transplants were performed until August 2023 [1]. Over the past few decades, survival rates for SOT recipients (SOTRs) have improved as a result of developments in surgical procedures and immunosuppressive regimens. These vulnerable patients are affected by in-

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vasive infectious diseases, which are more severe and involve a more diverse range of agents than in the general population [2]. Risk factors that predispose to infections in transplant recipients can be classified as those present in the recipient or donor prior to transplantation and secondary to intraoperative and post-transplant events. The timing of specific infections after SOTRs is generally predictable regardless of which organ is transplanted. The majority of clinically significant infections occur within the first 180 days; Individual pathogens typically emerge at stereotypical times after transplantation. However, the time of onset of some pathogens may be affected by the use of prophylactic strategies, changes in immunosuppression, or the need for additional surgical intervention. When assessing potential causes of infection in SOT recipients, it is useful to divide periods of risk into three main ranges to assess which pathogens are most likely: (a) early (0-30 days post-transplant); (b) medium (30-180 days) and (c) late (more than 180 days). However, this evaluation based on time is not absolute. Some infections may occur in the post-transplant period, while others may occur outside of the usual risk periods. However, consideration of these time intervals provides a useful framework for approaching a patient with post-transplant fever and guides the initial differential diagnosis [3].

Retrospective cohort studies describing the epidemiology, clinical and outcome of the infections in the SOTRs are limited [3,4]. Infections are one of the leading causes of death in SOTRs. However, little is known about the incidence, epidemiology and clinical significance of infectious diseases in this population.

Vaccination, surgical prophylaxis, universal coverage, preemptive or pre-symptomatic treatment, targeted therapy, education, and avoidance are all preventive strategies that have been used in SOT recipients.SOT patients are a challenging group of patients with multiple etiologies due to the underlying immunosuppression. It is important for patient survival to be aware of the infections that can occur in this patient group. The prevention, diagnosis, and treatment of infectious diseases make important contributions to clinical organ transplantation. The emergence of transplantation infections as a specialty of infectious diseases has paralleled the prolongation of organ transplantation, prolongation of allograft and patient survival, and increasingly effective immunosuppressive agents [4].

This study aimed to evaluate and discuss common infectious diseases in patients with a history of liver or kidney transplantation and infectious diseases. All patients in our study include late-stage transplantation infections.

METHODS

Patients older than 18 years of age who underwent liver and kidney transplantation between 2011 and 2022 and were hospitalized in our hospital due to heart failure and for whom infectious diseases consultation was requested were retrospectively analyzed from hospital records. Demographic information, intensive care unit records, types of infection, microbiological investigations, other laboratory data, and radiological examinations of 32 consecutive patients were obtained.

The study was approved by Kosuyolu Yüksek İhtisas Training and Research Ethics Committee (Decision No: 2023/06/682, Date: 04/04/2023).

Statistical Analysis

Mean ± standard deviation, median (minimum, maximum), frequency, and ratio values were used in determining the descriptive statistics of the data.

RESULTS

Of the patients included in the study, 9 (28%) were female, 23 (72%) were male, and the mean age was 33.7±11.3 years (range: 17-66 years). Our patients' median age was 60 years. Fourteen patients (14%) over 65 years of age were observed. Patients had similar comorbidities. Patients had congestive heart failure (CHF) (87.2%, n = 28), hypertension (43.7%, n = 14), and chronic obstructive pulmonary disease (21.8%, n = 7) (Table 1).

In this retrospective study, 20 patients (62.5%) of kidney transplant recipients and 12 (37.5%) of liver transplant recipients were seen within ten years. The most common infections were urinary tract infections (UTIs) in 8 (25%) patients and pneumonia in 11 (34%) patients. The other infections were gastrointestinal infections such as diarrhoea, bloodstream infections and

Table 1. The characteristic of 32 transplant patients

Characteristic	Data
Age (years) (mean ± SD)	33.7 ± 11.3
Gender, n (%)	
Male	23 (72)
Female	9 (28)
Type of transplant, n (%)	
Kidney	20 (62.5)
Liver	12 (37.5)
Hospital admissions, n (%)	
Non-ICU	15 (46.5)
Direct to ICU	17 (53.5)
Primary sites of infection, n (%)	
Pneumonia	11 (34.3)
Urinary tract infection	8 (25)
Bloodstream infection/Bacteremia	6 (18.7)
Enteritis	3 (9.2)
COVID-19	3 (9.2)
CMV	1 (3.1)
Co-morbidities, n (%)	
CHF	28 (87.2)
DM	3 (9.2)
HT	14 (43.7)
COPD	7 (21.8)

ICU = intensive care unit, CHF = Congestive Heart Failure, DM = Diabetes Mellitus, HT = Hypertension, COPD = Chronic obstructive pulmonary disease, CMV = *Cytomegalovirus,* SD = standard deviation

Table 2. Classification and percentage of organisms from patients

Organism Isolated	Strain (n = 20) n (%)
Escherichia coli	5 (25%)
Enterococcus spp.	2 (10%)
Streptococcus pneumoniae	4 (20%)
Staphylococcus aureus	4 (20%)
Klebsiella pneumoniae	2 (10%)
Cytomegalovirus	1 (5%)
Candida albicans	2 (10%)

COVID-19 and *Cytomegalovirus* (CMV). All patients were found to have an infection. Culture positivity was found in 20 (62.5%) of 32 patients who presented with infection (Table 2).

The microbiological data were noteworthy for unusual and opportunistic organisms, including one instance of acute CMV viremia.

Severe sepsis and organ failure occurred in six (18.75%) of the 32 patients with documented infections. The patients had more than one accompanying comorbidity. Four (66%) of these six patients were diagnosed with cardiovascular dysfunction, four (66%) with acute renal dysfunction, and three (50%) with severe metabolic acidosis. With 17 (44%) patients, CHF was the predominant reason for the intensive care unit admission. As a result, six (18.7%) patients died after hospitalization. In our study, the pneumococcal vaccination rate was calculated as 9.3%. All of our patients wer late transplant patients (2 years-23 years). There were eight (25%) patients between 2 years and 10 years, 20 (62.5%) patients between 10 and 20 years and 4 (12.5%) patients over 20 years.

DISCUSSION

Despite significant improvements in patient and graft survival in the post-transplant period, it remains a significant cause of morbidity and mortality. To prevent graft rejection, transplantation patients are lifelong immunocompromised hosts due to immunosuppressive drug regimens. This excessive immunosuppression increases the potential for infections with common and opportunistic pathogens. The early signs of infection may be mild because of a suppressed inflammatory reaction to the infection, and these infections can be fatal in this state [5, 6]. In our study, six of thirty-two patients had a mortal course.

The majority of clinically significant infections are seen in the first 180 days. Six months after transplantation, most recipients are clinically stable, and immunosuppressive therapies are reduced. However, community-acquired infections are more common in this period [7, 8].

This is expected due to the high number of renal transplant patients seen and their high incidence of

UTIs. Many authors report that the frequency of UTI is higher in the early years after transplant, especially in the first year (74 %), while the frequency of UTI decreases to around 35 % in the second year and further to 21 % in the four years after transplant. In the later period, while immunosuppression continues, infections specific to the general population, such as UTIs with community pathogen aetiology, are more frequent [9]. In a large retrospective cohort study by Abbott *et al*. [10], the cumulative UTI rate after kidney TX was found to be 60% for women and 47% for men after four years. Only 17% of patients develop early UTIs in the first three months. Over 70% of all UTIs following renal transplantation are caused by Gram-negative organisms, with *Escherichia coli* being the most common organism in the general population (30 to 80%) [11, 12]. *E. coli* (54.2%) was the most common organism isolated from infected patients in the study [10].

In our study, we found *E. coli*, *Enterococcus* spp and *Candida albicans* as common Bloodstream infections (BSI) are the leading causes of SOT deaths and illnesses. While pathogens, gram-positive bacteria, are the most common cause of BSIs, Gram-negative bacteria are more common in renal transplant recipients and are primarily associated with UTIs [13, 14]. In our patient group, six patients were followed up due to bacteraemia and the source of the disease was observed to be the lung and urinary system. In the blood cultures of our patients, *E. coli* was found in 4 patients, *Staphylococcus aureus* in 1 patient and *Enterococci* with *Candida albicans* in 1 patient. The literature has reported that urinary tract infections and lower respiratory tract infections due to ventilation have emerged as the source of bacteremia, as in our study [15]. Sepsis is a severe complication of SOT. One study found that transplant patients were admitted to the intensive care unit for life-threatening complications. 24% of these were urinary tract infections [16-18]. Chuang *et al*. [19] Reported that 90% of transplant recipients who died of sepsis had UTI. The primary focus of infection in 2/3 of our patients who died due to sepsis was the urinary system.

Diarrhoea is common after transplantation, with a prevalence of 20% to 50% in solid organ transplant recipients, and the infectious agents are similar to those in non-transplant populations, but the presentation can be more severe. Diarrhea in this population can lead to dehydration, increased drug toxicity, organ rejection, and death [20, 21]. Immediate stool culture and toxicology are essential in such cases. *Clostridium difficile* infection (CDI) incidence rates in transplant recipients vary from 1% to 23%. The most critical risk factor for developing CDI is antibacterial exposure. Risk factors specific to the SOT population include age> 55 years, the use of anti-thymocyte globulin, retransplantation and the type of organ transplanted. The highest CDI rate is found in liver transplant recipients [22]. In our study, three patients had gastroenteritis. In two of these three patients, CDI caused diarrhoea in our transplant recipients.

The COVID-19 pandemic caused everyone to apply to the hospital, and many were hospitalized and treated. The rate of COVID-19-related hospitalization was higher in the solid organ transplant patient group than other patients [23]. Several comorbidities have been studied which impact the severity of COVID-19 disease. SOT patients have been identified as a risk group for COVID-19. This is due to their chronic immunosuppressive therapy. In a systematic review, age, post-transplantation time and comorbidity were variably identified as independent risk factors for mortality or disease severity.

SOT recipients show similar humoral and cellular immune responses after COVID-19 infection. SOT recipients have a decreased immune response after two doses of the SARS-COV-2 mRNA vaccine [24]. We conclude that the overall outcome was similar to the general population, based on another review and meta-analysis [20]. There were 3 COVID-19 patients in our study, 1 of whom died.

Prophylaxis after SOT is effective in the prevention of CMV infection during the period when patients are on antiviral therapy. Therefore, after the end of prophylaxis, CMV infection is usually observed [20]. Adult CMV-seronegative recipients transplanted from CMV-seropositive donors are the highest-risk group [25].

In another study, 37% of patients developed late-onset CMV infection on average 67 days after discontinuation of prophylaxis (range 1-475 days) and 244 days after transplantation (range 150-655 days) [26]. Considering that CMV disease occurred in our patient two years after transplantation, it would not be wrong to define our patient in the classification of late-onset primary CMV infection.

During the study period, %53 SOT were admitted to our ICU, of which 40% were admitted for sepsis, %26 for pneumonia, %40 for urinary tract infection, one for COVID-19, and one for acute gastroenteritis.

Limitations

The primary limitation of this study is the retrospective methodology. The patients are older than 18 years of age have had transplantation in external centers and have been hospitalized in our hospital for various reasons. Therefore, they were evaluated only with infectious diseases consultation.

CONCLUSION

Infection prevention has become a keystone of modern transplantation medicine due to the significant incidence of post-transplant infectious complications from improved immunosuppressive therapies and surgical procedures. This is essential to decrease the morbidity and mortality directly attributable to infection and reduce the burden of infection-related indirect effects contributing to impaired long-term allograft survival.

Authors' Contribution

Study Conception: SDK, GE; Study Design: SDK, GE; Supervision: SDK, GE; Funding: SDK, GE; Materials: SD, GE; Data Collection and Processing: SDK, GE; Statistical Analysis and Data Interpretation: SDK, GE; Literature Review: SD, GE; Manuscript Preparation: SD, GE, MD, YUK and Critical Review: SD, GE, MD,YUK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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