Infections developing in patients undergoing liver transplantation: Recipients of living donors may be more prone to bacterial/fungal infections

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ABSTRACT

Background/Aims: Despite surgical advances in liver transplantation and effective prophylactic strategies, posttransplant infections are the most important cause of morbidity and mortality. Diagnosis and management of infections because of developing immunosuppression is difficult and adversely affects mortality. This study aimed to review bacterial and fungal infections in patients after liver transplantation and to reveal the resistance rates.

Materials and Methods: A total of 107 patients who underwent liver transplantation between January 2017 and February 2018 were evaluated retrospectively with regard to demographic characteristics, causes of transplantation, conditions that may lead to infection, postoperative infections, pathogens, and resistance patterns.

Results: Of the 107 patients who underwent liver transplantation, 48 (44.8%) had an infection. Bacterial infections were detected in 41% of the patients, and fungal infections were found in 13%. When we compared living and cadaveric transplants in terms of infection development, these rates were found to be 53% and 33%, respectively (p=0.034). No statistically significant results could be obtained when evaluating conditions such as sex, presence of underlying primary disease, Model for End-Stage Liver Disease MELD score, diabetes status, total parenteral nutrition, and risk factors for infection.

Conclusion: After liver transplantation, infections are often seen in the first month of the postoperative period. Knowing the most common pathogens and resistance states in this process reduces infection-related deaths by providing appropriate treatment regimens at the right time.

Keywords: Liver, liver transplantation, living donor liver transplantation, post-transplant infection

INTRODUCTION

Liver transplantation is the main treatment option in acute or chronic liver failure and also an important treatment option for patients with primary liver malignancies (1). Liver transplant recipients are at high risk of infection, with estimates of up to 80% (2). In recent years, better surgical methods, introduction of new immunosuppressive agents, efforts for early diagnosis, and prevention of infectious agents have helped to increase the survival rates of these groups of patients to above 85%. Newly developed surgical techniques and immunosuppressive treatments have increased survival rates and prevented the long-term complications owing to infection; however, morbidity and mortality rates remain high (3, 4).

In a study assessing the autopsies to investigate the reasons underlying posttransplant deaths, it was found that 64% of 321 deaths were because of infections, of which

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48% were caused by bacterial agents, 22% by fungal agents, and 12% by viral agents (5).

In this study, the patients who were followed up and monitored by our hospital's transplantation center and who underwent liver transplantation between January 2017 and February 2018 were retrospectively studied in terms of posttransplant infection development. They were assessed for demographic characteristics, causes of transplantation, and conditions that could lead to infection, and we aimed to investigate the infection foci, common agents, resistance patterns, and mortality rates of the patients developing infection.

MATERIALS AND METHODS

One hundred seven patients undergoing liver transplantation and 1 patient undergoing retransplantation, that is, a total of 108 transplantations were retrospectively assessed in terms of demographic characteristics, causes of transplantation, postoperative infection development, and conditions that could lead to infection. Patients developing infection were assessed with respect to hospital-acquired pneumonia, bloodstream infection, intraabdominal infections, and urinary tract infections in accordance with the diagnostic criteria described in the guidelines (6-10). All the microbiological cultures were done in the Bacteriology Laboratory of Ege University Hospital according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. Aerobic and anerobic blood bottles were incubated in BacT/Alert 3D System (BioMeriéux, Durham, NC, USA). All isolated microorganisms were identified using conventional biochemical procedures and MALDI-TOF Vitek MS (Bio Meriéux Inc., Mercy L'Etoile, France). Antimicrobial susceptibility testing was done by automated system VITEK 2 (BioMeriéux, Marcy-l'Etoile, France) and evaluated according to EUCAST criteria. Risk factors for the patients with and without infection development were compared statistically. In patients who developed infection during follow-up, the infection foci, the causative microorganisms, and the antibacterial resistance patterns were examined. We also analyzed and compared our findings with our hospital's resistance profile.

MAIN POINTS

- *Despite the advances in liver transplantation, morbidity and mortality ascribable to infectious complications continue to be an important problem and in many centers, infection after liver transplantation is the most common cause of death.*
- *Bacterial infections are frequently encountered within the first month after transplantation.*
- *Our study demonstrated that presentation of an infection at any time after transplantation significantly increased mortality.*
- *Assessment of the immunosuppression status of each patient undergoing transplantation and knowledge about hospital infection agents at the transplantation center and their resistance will facilitate diagnosis, treatment, and management of infections, thereby reducing the number of deaths attributable to transplantations.*

Statistical Analysis

Chi-squared test was used in data analysis, and $p<0.05$ was considered significant.

RESULTS

Of 107 patients undergoing liver transplantation (with 1 patient undergoing retransplantation, a total of 108 transplantations), 48 (44.8%) developed infection within 1 year after the transplantation. Of the 48 patients, 41% were diagnosed with bacterial infection, 13% with fungal infection, and 11.2% with mixed infection, and infection development rates were noted to be 53.9% (34/63) and 33.3% (15/45) in living donor and cadaveric donor transplants respectively (p=0.034). The most common infection was revealed to be bloodstream infection in 27.7% (50% secondary, 33.3% primary, and 16.6% central venous catheter–related bloodstream infections), followed by intraabdominal infections in 25%, hospital-acquired pneumonia in 21.2%, and urinary tract infections in 10.1% of the patients.

The agent most commonly isolated from blood culture was found to be Enterococcus faecium. Bacteremia is frequently encountered after living donor transplants (p=0.006). All cases of bacteremia owing to Acinetobacter baumannii were detected in transplantations from cadaveric donors. Respiratory tract infections and intraabdominal infections were significantly more frequently monitored in transplantations from living donors (p=0.009 and p=0.000, respectively); no statistically significant difference was obtained for urinary tract infections (p=0.054) (Table 1).

Patients with and without infection development were compared in terms of conditions such as sex, causes of transplantation, MELD score, diabetes, and presence of total parenteral nutrition (TPN), dialysis, and prolonged hospitalization in intensive care unit, which may constitute the risk factors for infection development. Dialysis and a history of prolonged hospitalization in intensive care unit were found to be statistically significant factors in

Table 1. Distribution of variables according to the presence of infection.

Variable		Infection	No infection	Total
Sex	Female	28	23	51
	Male	20	36	56
	Total, n (%)	48 (44.8%)	59 (55.2%)	107
Age, years	<18	14	4	18
	18–65	31	44	75
	≥65	3	11	14
	Total	48	59	107
Causes of transplantation	Congenital	5	0	5
	Metabolic	7	4	11
	Viral hepatitis	11	10	21
	Malignancy	5	13	18
	Fulminant failure	3	0	3
	NASH	2	6	8
	Autoimmune	6	2	8
	Vascular pathology	0	5	5
	Toxic hepatitis	1	4	5
MELD score*	≥25	16	17	33
	24–19	21	30	51
	18–11	11	7	18
	≤10	1	5	6
	Total	49	58	107
Types of transplantation**	Living donor	34	29	63
	Cadaveric donor	15	30	45
		49	59	108
Diabetes	Yes	9	10	19
	No	39	49	88
Use of TPN	Yes	4	4	8
	No	44	55	99
History of dialysis	Yes	4	0	4
	No	44	59	103
History of prolonged intensive care unit hospitalization ***	Yes	23	6	29
	No	25	53	78
Mortality	Alive	28	50	78
	Exitus		20	9

*MELD score of the patient undergoing transplantation twice was 17 at the first transplantation and 41 before the retransplantation.
**One patient underwent transplantation twice; one from a living donor and the other from a cadaveric donor.
***Patients with a length of stay in the intensive care unit exceeding 2 days were included.
NASH: Nonalcoholic steatohepatitis.

Table 2. Distribution of bacterial infections and agents according to whether transplanted from a living or a cadaveric donor.

Bacterial infections*			Living	Cadaveric	Total	p
Bacteremia	*Enterococcus faecium*		6	3	9	
	Escherichia coli		6	0	6	
	Acinetobacter baumannii		0	5	5	
	Klebsiella pneumoniae		5	0	5	
	Pseudomonas aeruginosa		3	0	3	
	Providencia stuartii		0	2	2	
	Bacteremia Yes		20	10	30	0.006
	No		29	49	78	
	Total transplantations		49	59	108	
Hospital-acquired pneumonia	*Acinetobacter baumannii*		4	3	7	
	Pseudomonas aeruginosa		5	1	6	
	Klebsiella pneumoniae		4	2	6	
	Staphylococcus aureus		2	0	2	
	Corynebacterium striatum		1	1	2	
	Growth	Yes	16	7	23	0.009
		No	33	52	85	
	Transplantation		49	59	108	
Intraabdominal infections	*Enterococcus faecium*		10	1	11	
	Pseudomonas aeruginosa		8	0	8	
	Acinetobacter baumannii		2	1	3	
	Klebsiella pneumoniae		3	0	3	
	Escherichia coli		2	0	2	
	Growth	Yes	25	2	27	0.000
		No	24	57	81	
	Transplantation		49	59	108	
Urinary tract infections	*Enterococcus faecium*		2	3	5	
	Escherichia coli		4	0	4	
	Pseudomonas aeruginosa		2	0	2	
	Growth	Yes	8	3	11	0.054
		No	41	56	97	
	Transplantation		49	59	108	

*The agents showing growth in more than 2 patients are included in the table.
**Multiple agents were isolated from the repeated cultures of 20 patients.

the development of posttransplant infection (p=0.0037 and p<0.0001, respectively). The average MELD score for 108 transplantations was found to be 22.76 (minimum=4, maximum=41 ±7.24)

It has been demonstrated that an infection developing at any time after transplantation significantly increased mortality (p=0.004) (Tables 2 and 3).

In our study, 16% (4/25) of the enterococci isolated from blood, intraabdominal samples (drains, abdominal puncture fluids, and abscess cultures), respiratory tract samples, and urine cultures (4/25) were found to be vancomycin-resistant, and 40% (2/5) of the staphylococci were methicillin resistant; 92.5% (25/27) of the gram-negative bacteria produce extended-spectrum beta-lactamases. Escherichia coli was found to be sensitive

Table 3. Distribution of fungal infections and agents according to the donor being either a living or a cadaveric donor.

Fungal infections*		Living	Cadaveric	Total
Blood	*Candida albicans*	3	0	3
	Trichosporon asahii	1	0	1
Hospital-acquired pneumonia	*Candida albicans*	1	0	1
	Trichosporon asahii	1	0	1
Intraabdominal infections	*Candida albicans*	6	0	6
	Candida glabrata	1	0	1
	Candida tropicalis	2	0	2
	Trichosporon asahii	1	0	1
	Candida dubliniensis	1	0	1
Urinary tract infections	*Candida albicans*	1	0	1
	Candida glabrata	1	0	1
	Candida guilliermondii	1	0	1
	Trichosporon asahii	1	0	1

*In 3 patients, fungal agents were isolated from multiple samples.

to carbapenem (0/12), and resistance to carbapenem was determined to be 100% (15/15), 47% (7/15), and 63.1% (12/19) of A. baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae strains, respectively.

After transplantation, fungal infection was found in 14 patients, and Candida spp. infections ranked first among these infections and were isolated from all living donor transplantations. In all samples, the most frequently isolated strain was C. albicans. Resistance to voriconazole was detected only in 1 C. albicans strain isolated from the intraabdominal abscess culture. No azole resistance was found in other strains. In a pediatric patient, Trichosporon asahii was isolated from all blood, urine, and intraabdominal drain cultures, and resistance to fluconazole and anidulafungin and sensitivity to itraconazole were established in antifungal sensitivity studies.

DISCUSSION

Today, solid organ transplantation has become a routine treatment method for not only end-stage heart, kidney, lung, pancreas, and small intestine diseases, but also end-stage liver failure (3).

The success of transplantation is not only limited to prevention of rejection through surgical methods and appropriate immunosuppressive treatments but also successful infection management, which plays a critical role in this process. In the literature, an annual survival rate of 75%–80% is reported after transplantation in Germany, 92% in United Kingdom, 87% in Turkey, 79% in Japan, and 85% in the United States (11-15). As the lifespan extends, the frequency of infections increases. Because of the complexity of the surgical procedures comprising hepatobiliary system penetration, the ratio of bacterial infection development is known to be higher after liver transplantations, compared with other solid organ transplantations (16). In this study, approximately 44% of the patients developed infection within 1 year following transplantation. In the literature, infection rates varying from 14.1% to 67% are reported in transplantation centers (17-19). In our study, especially the frequency of bacterial infections within the first month is significant and in accordance with the literature. However, when compared with other centers with lower incidence of infection, the relatively higher rates of infection in our center may be attributable to a higher number of transplantations from living donors, admission of more patients with complex cases on account of being a regional hospital, lack of isolation rooms for transplantation patients, and insufficiency of infrastructure. In the study conducted by Avkan-Oğuz et al. (20) the incidence of infection was found to be 37% (38.7% deceased donors and 61.3% living donors), and the most common infections were reported

to be the surgical ones by a rate of 20.2%. These were followed by a rate of 17.4% of bloodstream infections, 13.4% lung infections, and 7.1% urinary tract infections (20). In our study, when the infection foci were analyzed, bloodstream infection was found to be the most common infection, followed respectively by intraabdominal infections, respiratory system infections, and urinary tract infections.

It is important to determine the risk of developing an infection after transplantation. Many variables, for example, the dose and duration of immunosuppressive treatment, presence of catheters, provision of appropriate nutrition for the patient, metabolic state, immunomodulatory viral infections, graft infections, and underlying diseases play a role in determining the risk of infection (21). A pretransplant MELD score of >30, need for a second operation, posttransplant renal replacement therapy, and a duration of stay longer than 48 hours in intensive care unit are other important risk factors (22). In the study conducted by Avkan-Oğuz et al. (20) which analyses 367 patients, factors such as transplantation from cadaveric donors, a MELD score of >20, an albumin level of <2.8 g/dL, intraoperative infusions of >6U erythrocyte suspension and >12U fresh frozen plasma, bilioenteric anastomosis, a duration of hospitalization of more than 6 days in the intensive care unit, and a hospitalization duration of more than 21 days in the postoperative process were found to be significant risk factors in terms of development of bacterial infection within the initial 30 days after transplantation (20). In our study, we found that posttransplant dialysis and a history of a prolonged stay in the intensive care unit were demonstrated to be statistically significant factors in the development of posttransplant infection. When 107 patients were analyzed in terms of MELD score, 84 patients were documented to have a MELD score of >20, and 44% of these patients were seen to have developed bacterial infection. However, no association was uncovered with MELD score, presence of diabetes, and use of TPN. It was considered that these results could be accounted for by the small number of patients with TPN use and a history of diabetes in our patient population.

Nevertheless, the differences between transplantations from living donors and those from cadaveric donors in terms of posttransplant infection development are yet to be clarified in the literature. In our study, the infection development rate was found to be higher in transplantations from living donors than that in transplantations from cadaveric donors. In particular, intraabdominal infections were found to be more frequent in transplantations from living donors. In a retrospective study by Ki et al. (19) in Korea, on assessment of all infection complications, infection development rates were found to be similar in transplantations from both cadaveric and living donors by the rates of 67.7% and 67%, respectively. In subgroup analyses, intraabdominal infections were found to be more common in transplantations from living donors (19). Besides, in a study analyzing 55 patients undergoing transplantation from living donors and 173 patients undergoing transplantation from cadaveric donors between January 2003 and December 2006, lung infection was found to be significantly more frequent in transplantations from living donors (18%–5%), and the risk of bloodstream infection was also observed to have increased in living donors (33%–21%) (23). In another study, 611 patients were evaluated retrospectively, and no difference was found in the infection rates between both transplantations from living and cadaveric donors, but they did not evaluate subgroup analysis, such as infection types. However, in this study, posttransplant complications such as hepatic artery thrombosis and biliary-related conditions were reported to be more common in transplantation from living donors (24). In our study, the rate of intraabdominal complications of patients who developed posttransplant infection was 64.7% (22/34) and 33.3% (5/15) in living donor and cadaveric donor transplants, respectively. We suggested that the high complication rate in patients who underwent transplantation from living donors could explain the high rate of infection in our study.

Of the agents leading to posttransplant bloodstream infection, enterococci ranked first, and in respiratory tract samples, Acinetobacter spp. ranked first in keeping with our hospital's infectious agent profile. In a study analyzing 233 patients undergoing liver transplantation between the years of 1989 and 2003, gram-negative bacteremia rates that were found to be 25% between 1989 and 1993 rose to 51.8% in the following 10 years, whereas the gram-positive bacteremia rates were observed to have decreased from 75% to 48% (25). Of the 75 patients undergoing liver transplantation between January 2008 and July 2011, 21 (28%) developed bloodstream infection, and 52.3% of the isolated agents were found to be gram-negative bacteria (predominantly K. pneumoniae and P. aeruginosa), 47.7% of those were established to be gram-positive bacteria. Of these, most consisted of coagulase-negative staphylococci and Staphylococcus aureus (26). Vancomycin resistance rate of enterococci is also comparable with that of our hospital infection

agents. Again, the rate of extended-spectrum beta-lactamase synthesis (ESBL) and carbapenem resistance of the gram-negative agents isolated in this group are consistent and compliant with resistance rates determined by Erdem et al. (27) in hospital infection agents, which suggests that in this group, the use of third generation cephalosporins in the prophylactic or preoperative periods as well as the use of piperacillin/tazobactam for a short period of time for treatment may be associated with high ESBL rates in gram-negative agents across the hospital.

Invasive fungal infections developing in the aftermath of orthotropic liver transplantation have started to appear as a more common cause underlying the high mortality and morbidity rates. Studies illustrate that 5%–42% of the patients undergoing liver transplantation develop at least 1 fungal infection after transplantation. Mortality rates ranging from 25% to 69% have been reported in the literature (28). In such groups of patients, *Candida* spp., Aspergillus spp., and Cryptococcus spp. are the most frequently isolated pathogens (28). It is an important shortcoming that antifungal sensitivity has not been studied for all for C. spp. isolated in our study. When strains that could be investigated for sensitivity were analyzed, voriconasole resistance was detected in only 1 C. albicans strain. Trichosporonosis is a rare fungal infection documented in a pediatric patient through growth in all cultures following transplantation. These types of infections have high rates of mortality attributable to delayed diagnostic process and in vitro and in vivo differences in sensitivities of the antifungal agents (29). Unfortunately, despite the antifungal therapy, just like the other patients reported, our patient had also deceased (30, 31).

In conclusion, despite the advances in liver transplantation, morbidity and mortality ascribable to infectious complications continue to be an important problem. In many centers, infection after liver transplantation is the most common cause of death. In our hospital, although bacterial infections were noted within the first month, commonly after transplantations from living donors, the fungal infections were also significantly high. Our study demonstrated that presentation of an infection at any time after transplantation significantly increased mortality. Assessment of the immunosuppression status of each patient undergoing transplantation and knowledge about hospital infection agents at the transplantation center and their resistance will facilitate diagnosis, treatment, and management of infections, thereby reducing the number of deaths attributable to transplantations.

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