Original Article

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Bacterial Infections Post Liver Transplantation; One Year Experience

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Abstract

In adults with acute and chronic end-stage liver disease, liver transplantation (LT) is the only treatment option for these patients. On the other hand, one of the substantial causes of death in these patients is bacterial infection after transplantation, which should be considered as well as appropriate antibacterial treatment. For this reason, this study was designed to provide a multi-faceted review of different types of infections after transplantation and their treatment options during one year of experience in the largest LT center for adult patients in Iran. In this retrospective cohort study, records from all individuals over 18 years of age candidates for liver transplantation in Abu-Ali Sina hospital, Shiraz, Fars, Iran from 2018 March to 2019 March , were assessed. Demographic, laboratory, and clinical data were extracted in addition to the antimicrobial therapy. In this study, 412 patients included. 15.77% of patients were infected after transplantation, of which 61.17% of the isolated pathogens were gram-negative and 38.83% were gram-positive. The most common isolated gram-positive and gram-negative microorganisms include staphylococci (27.69%) and Klebsiella (27.69%), respectively. Urinary tract infection was the most common type of infection after transplantation in adult liver transplant recipients, and length of stay in ICU, length of hospital stay, length of mechanical ventilation are among the risk factors affecting bacterial infection after LT.

Keywords: Liver transplant, bacterial infections, antibiotics.

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1. Introduction

Globally, liver disease (LD) is one of the most leading cause of morbidity and mortality (1). LD is responsible for almost two million deaths per year (2). The most significant factors causing liver failure in adults include primary biliary cirrhosis, primary sclerosing cholangitis, nonalcoholic fatty LD (NAFLD), alcoholic LD (ALD), and viral hepatitis (3, 4).

Liver transplantation (LT) is currently the only effective strategy to improve survival in patients with liver failure (5). In spite of remarkable advances in LT, infection is one of the main risk factor in terms of morbidity and mortality after transplantation (6, 7). Relatively, it is stated that post-liver transplant infections occur in more than 50% of LT recipients (8). The main type of infection after LT is bacterial, followed by fungal and viral infections. The probability of getting bacterial infections after LT is high for various reasons such as the complexity of the surgical procedures and medical complications such as the use of immunosuppressive drugs (7, 9). In general, the most

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common types of infections after LT comprise surgical site infections (SSIs), deep intra-abdominal infections, pneumonia, bacteremia, urinary tract infections, and catheter-related infections (10).

As a result, evaluating the pattern of infection in LT recipients is crucial. This retrospective study was conducted to investigate different aspects of bacterial infections including type, number and risk factors of infection the antibiotic regimens used and finally comparing the antibiotic regimens in terms of success rate or treatment failure in adults undergoing LT in a referral transplantation center in Iran.

2. Methods

2.1. Study Design and Patient Population

This study is a single-center, cross-sectional with a retrospective approach. In this study, the medical file of all liver transplant recipients in ABu Ali Sina organ transplant Hospital, Shiraz, were studied from March 21, 2018 to March 20, 2019. The inclusion criteria were patients over 18 years old and hospitalized for at least 48 hours after LT. Individuals undergone simultaneous LT and kidney were excluded from the study.

Medical and laboratory records of all patients were extracted from the electronic information system available in the hospital and reviewed by a pharmacist under the supervision of clinical pharmacists.

Demographic data such as age, gender, cause of liver failure , body mass index (BMI), end-stage Liver disease score model (MELD) (11) and previous history of receiving and using antibiotics within one week to three months before LT were recorded. LT technique (including the joining of the recipient vein inferior vena cava (IVC) to the donor IVC (Piggyback) for IVC reconstruction and biliary reconstruction performed via a duct-to-duct choledochochoedochostomy or Roux-en-Y hepaticojejunostomy), mean operating time, immunosuppressive regimens, duration of ICU and hospital stay, re-hospitalization, rejection or re-transplantation and clinical results after transplantation were also investigated.

The Medical Ethics Committee of Shiraz University of Medical Sciences approved the study (ethical code: IR.SUMS.REC.1399.029). All protocols were performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (12).

2.2. Antibiotic Prophylaxis regimen

All patients were taking antibiotic prophylaxis for surgical site infection including ceftizoxime (2 gr IV Q8h) and ampicillin-sulbactam (1.5 gr IV Q6h) until 72 hours after LT.

To prevent Pneumocystis jirovsi, all patients were received trimethoprim/sulfamethoxazole (480 mg QD for 365 days) .Fluconazole (150 mg QD for 30 days) was given to prevent fungal infections, and only for patients who have a positive cytomegalovirus (CMV) PCR, valganciclovir or ganciclovir was given as a treatment.

2.3. Immunosuppressive Regimen

The maintenance immunosuppressive regimen includes a combination of mycophenolate mofetil, tacrolimus, and prednisolone. The dosage of these agents were adjusted according to the condition of the transplant graft, the plasma level of the drug, and also the time elapsed after LT.

2.4. Microbiological Assessment

Monitoring microbiological cultures of blood, sputum, urine, and abdominal fluid were performed based on clinical and laboratory outcomes. If the patients suspect infection, necessary measures were done. They include chest and abdominal radiographs, examination of inflammatory factors such as C-reactive protein, red blood cell sedimentation rate, procalcitonin, complete red blood cell count, and urine as well as sputum cultures were performed. In this study, the classification of infections was based on the CDC/NHSN surveillance classification of healthcare-associated infections (13). In this study, disk diffusion test was the selected test by which the antibiotic resistance/susceptibility results were evaluated.

2.5. Definition of Antibiotic-resistant Bacterial Species

The identification of multidrug-resistant (MDR), extended drug-resistant (XDR) and pandrug-resistant bacteria is according to The European Centre for Disease Prevention and Control`s

Consensus Statement (14). The concept of MDR is describe as lack of sensitivity to at least one agent in three or more antimicrobial classes, and XDR is explained in being non-susceptible to at least one agent in all but two or fewer antimicrobial groups (14).

2.6. Statistical Analysis

Descriptive-analytical statistical analyzes were performed on the available data of all individuals. Statistical analysis was done using the SPSS software. Descriptive statistics were presented as mean±standard deviation and proportions as appropriate. Chi-square test was used to compare classification data. The statistical tests used in univariate analysis were t-test and Mann-Whitney test. Significant variables (P<0.05) in the univariate model were included in the multivariate linear regression. Possible relationship between different demographic, clinical and paraclinical characteristics of the study population and progress of infections was done by multivariate logistic regression test. Comparison of the effect of different experimental antibiotic regimens on white blood cells, body temperature, and CRP level in consecutive days after the start of antibiotic treatment was performed using one-way analysis of variance (ANOVA) with repeated measures. The level of statistical significance was set at $p<0.05$ for all of these tests.

3. Results

3.1. Demographic, clinical, and laboratory characteristics:

In this study, 412 patients over 18 years of age underwent LT were carefully examined for the duration of one year. Their average age was 48.35±12.23 years. Most (65.7%) of the cohort were male. In this study, 65 patients had at least one documented infection after LT, they were included in the infectious group, and the other 347 patients who did not have any signs/symptoms of infection were considered as the control group. Table 1 shows the demographic and clinical char-

Table 1. Demographic and clinical characteristics of the liver transplant recipients with and without bacterial infection.

Variable	Non-infectious patients (N:347)	Infectious patients(N:65)	P value
	Patient age (years)		
Mean ± standard deviation	46.56 ± 13.02	46.56 ± 13.02	0.457
	Gender (%)		
Female	119 (34.3)	35 (53.8)	
Male	228 (65.7)	30 (46.2)	
	Indications for liver transplantation (%)		
Hepatitis B	62 (17.9)	4 (6.2)	0.81
Hepatitis C	10 (2.9)	0 (0)	
Hepatocellular carcinoma(HCC)	5 (1.4)	0 (0)	
Cryptogenic	55 (15.9)	16 (24.6)	
Autoimmune Hepatitis	52 (15)	12 (18.5)	
Primary sclerosing cholangitis	67 (19.3)	9 (13.8)	
Primary biliary cholangitis	9 (2.6)	2 (3.1)	
Wilson Disease	13 (3.7)	2 (3.1)	
Non-Alcoholic SteatoHepatitis	33 (9.5)	5 (7.7)	
Budd-Chiari syndrome	5 (1.4)	3 (4.6)	
Cholangiocarcinoma	7 (2)	1 (1.5)	
Alcoholic	4 (1.2)	2 (3.1)	
Acute Liver Failure	10 (2.9)	6 (9.2)	
Other	15 (4.3)	3 (4.6)	

Continued Table 1.

	MELD Score		
Mean ± standard deviation	18.08±6.270	20.46±7.444	0.002
	Body mass index: BMI (kg/m2)		
Mean ± standard deviation	24.74±4.44	24.91±3.90	0.484
	(%):Underlying liver dx		
Diabetes	54 (15.6)	12 (18.5)	0.297
Hypertension	13 (3.8)	1 (1.5)	0.262
Asthma	4 (1.2)	0 (0)	0.433
Gastrointestinal Disorder	14 (4)	2 (3.1)	0.492
Ischemic Heart Disease	6 (1.7)	2 (3.1)	0.315
Gynecologic	7 (2)	1 (1.5)	0.610
Opium Addiction	4 (1.2)	1 (1.5)	0.567
Thyroid Problems	12 (3.5)	1 (1.5)	0.306
Other Medical Conditions	32 (9.2)	4 (6.2)	0.243
	History of antibiotic use (%)		
Yes	69 (19.9)	12 (18.5)	0.445
No	278 (80.1)	53 (81.5)	
	Exploration (%)		
Yes	47 (13.5)	17 (26.2)	0.002
No	300 (86.5)	48 (73.8)	
	Cytomegalovirus (CMV) (%)		
Yes	304 (88)	47 (72.3)	<0.05
No	61 (12)	18 (27.7)	
	Antibiotic prophylaxis regimen (%)		
Ampibactam + Ceftizoxime	237 (68.3)	54 (83.1)	0.003
Ampibactam + Gentamicin	110 (31.7)	11 (16.9)	
	Immunosuppressant drug regimen (%)		
Methylprednisolone	342 (98.6)	65 (100)	0.352
Thymoglobulin	5 (1.4)	0 (0)	
	Liver transplant rejection (%)		
Yes	59 (17)	16 (24.6)	0.055
No	288 (83)	49 (75.4)	
	Dialysis/CRRT		
Yes	36 (10.4)	18 (27.7)	<0.05
No	311 (89.6)	47 (72.3)	
	Mortality		
Yes	42 (12.1)	18 (27.7)	<0.05
No	305 (87.9)	47 (72.3)	
	Mortality due to infection		
Yes	15 (35.7)	11 (61.1)	0.004
No	332 (64.3)	54 (38.9)	
	Length of ICU stay (days)		
Mean ± standard deviation	8.32±6.685	14.55±11.669	<0.05

Continued Table 1.

Length of Hospital stay (days)			
Mean ± standard deviation	15.46±7.896	8.556±19.40	<0.05
Length of mechanical ventilation after liver transplantation (days)			
Mean ± standard deviation	3.98±6.12	4.03±6.003	0.07

acteristics of the cohort in two infectious and non-infectious groups. According to univariate logistic regression, gender (P value: <0.05) , MELD score (P value: 0.002) , history of hepatitis B virus (P value: 0.003), performing exploration (P value: 0.002) , cytomegalovirus (CMV) (P value: <0.05) , antibiotic prophylaxis regimen (P value: 0.003) , dialysis/CRRT (P value: <0.05) , thrombosis (P value: <0.05) , systemic inflammatory response syndrome. (SIRS) (P value: <0.05), length of ICU stay (days) (P value: <0.05), and length of hospital stay (days) (P value: <0.05) significantly associ-

Table 2. Laboratory data among liver transplant recipients with and without bacterial infections.

Variable	Non-infectious patients	Infectious patients	P value
	WBC (cells/Ml)		
Median	5800	7400	0.006
	Hb (g/dl)		
Median	11.800	11.800	0.423
	PLT (mcL)		
Median	95500	80000	0.275
	AST (U/L)		
Median	61	57	0.909
Upper and lower interquartile range	41-108	39-104	
	ALT (U/L)		
Median	44	40.50	0.902
	ALK-Ph (U/L)		
Median	351	349	0.727
	Total Billi (µmol/L)		
Median	3.86	5.4750	0.015
	Direct Billi (µmol/L)		
Median	1.64	2.57000	0.019
	Alb (g/dL)		
Median	3.100	2.900	
	INR		
Median	1.4900	1.6300	0.006
	Na (mmol/L)		
Median	138.00	136.00	0.010
Upper and lower interquartile range	134.00-141.00	132.75-140.00	
	BUN (mg/dL)		
Median	14.000	15.000	0.046
	Creatinine (mg/dL)		
Median	0.9000	0.9000	0.376
	FK Level (µg/L)		
Median	5.7000	6.4000	0.545
	Cyclosporine level (ng/mL)		
Median	73.550	107.650	1.000

Table 3. Type of isolated microorganisms among liver transplant recipients.

Type of Isolated Microorganism	Number of cases in infectious patients (n:65)
Staphylococcus	18 (27.69 %)
Staphylococcus epidermidis(MRCONS)	9 (50 %)
Staphylococcus epidermidis (MSCONS)	8 (44.44 %)
Staphylococcus aureus(MRSA , MSSA)	1 (5.55 %)
Enterococcus	12 (18.46 %)
VRE (Vancomycin-Resistant *Enterococcus*)	8 (66.67 %)
NOT VRE (Vancomycin-Resistant *Enterococcus*)	4 (33.33 %)
Streptococcus	10 (15.38 %)
Klebsiella	18 (27.69 %)
Carbapenem-resistant *Klebsiella pneumoniae* (CRKP)	15 (83.33 %)
Carbapenem-sensitive *Klebsiella pneumoniae* (CSKP)	3 (16.67 %)
Escherichia coli	15 (23.08 %)
Enterobacter	12 (18.46 %)
Acinetobacter	9 (13.84 %)
Pseudomonas	7 (10.77 %)
Citrobacter	2 (3.07 %)
Polymicrobial	24 (36.92 %)

ated with the development of post LT infection.

Table 2 lists laboratory data in adults receiving LT in two infectious and non-infectious groups. , the factors that are affected by infection include WBC, Total Bilirubin, Direct Bilirubin, serum Alb, Total Protein, INR, sodium, calcium, and BUN based on univariate logistic regression.

3.2. Infection Types, Infection Sites, and Isolated Bacteria

In total, more than 61.17% of the isolated pathogens are Gram-negative and the remaining 38.83% are Gram-positive. The most prevalent isolated microorganisms include Gram$^+$ *Staphylococcus* (n=18), Gram$^-$ *Klebsiella* (n=18), Gram$^-$ *Escherichia coli* (n=15), Gram$^+$ Enterococcus (n=12), and Gram$^+$ Streptococcus (n=10), and (Table 3).

The most common sites of infection were urine (n=23) and blood (n=15).

The classification of microorganisms based on the type of sensitivity or resistance to different antibiotics was demonstrated in Table 4.

Among the total number of patients infected, 63, 53, 22, and 6 cases were MDR, XDR, PDR bacterial species, and ESBL, respectively.

In the study population, some antibiotics were used as empirical; accordingly (Table 4), 99

Table 4. Comparison of the frequency and percentage of Empirical antimicrobial therapy among adults receiving liver transplants.

Type of antibiotic	number of cases	Duration of antibiotic use (Median)	range between the minimum and maximum days of antibiotics use
Vancomycin	47	7	5-9
FQs*	61	7	5-9
Carbapenem	37	7	6-8.5
Piperacillin+Tazobactam	47	7	5-8
Ampicillin+Sulbactam	6	7	5-9.25
Others	31	5	4-8

*FQs : fluoroquinolone

Table 5. Comparison of the frequency and percentage of Confirmed combined treatment regimen based on antibiogram in adults receiving liver transplant.

Type of antibiotic	Total number of items (65)	Duration of antibiotic use (Median)	range between the minimum and maximum days of antibiotics use
Vancomycin	26	7.5	5-12.25
FQs*	35	7.5	5-14
Aminoglycosides	13	7	5-9
Colistin	10	9	5-14.25
Carbapenem	30	8	5-11.25
Piperacillin+Tazobactam	27	8	6-11
Ampicillin+Sulbactam	9	8	5-10.5
Targocid(Teicoplanin)	14	6.5	4.75-9.25

*FQs:fluoroquinolone

cases received FQs (n=61), Vancomycin (n=47), Piperacillin+Tazobactam (n=47), Carbapenem (n=37), Ampicillin+Sulbactam (n=6) and other antibiotics (n=31).

Table 5 listed the frequency, percentage, and number of days of antibiotic use (median) as confirmed treatment regimen in the cohort. The antibiotics given were Fluoroquinolones (n=35), Carbapenem (n=30), Piperacillin-Tazobactam (n=27) , Vancomycin (n=26) , Teicoplanin (n=14) , Aminoglycosides (n=13) , Colistin (n=10) , and Ampicillin-Sulbactam (n=9)

4. Discussion

The frequency of bacterial infections after LT has decreased from the past until now. This change is due to different factors such as the use of preventive antibiotic regimens before transplantation, accelerating surgical procedures, optimal use of immunosuppressive drugs, and improving post-transplantation care (7). In this study, the incidence rate of bacterial infections after LT was 15.77%, which is in line with previous studies around the world, including Turkey (23.3%), Poland (27.2%), Korea (27.1%), and West China Hospital (14.01%) (15-17). Different factors can predispose a person to develop bacterial infections after transplantation such as high MELD score, underlying alcoholic liver disease, staying in the ICU for more than 2 days before transplantation, malnutrition, recipient age the use of internal urinary as well as vascular catheters, and bleeding from the gastrointestinal tract. (18-20)

The type of bacteria that lead to complication after transplantation are different (7). Enterobacteriaceae are gram-negative bacteria that cause various types of problems after transplantation, such as biliary leakage or obstruction, and most importantly, infection. Infections that can occur as a result of contamination by Enterobacteriaceae mainly include deep intra-abdominal infection, bacteremia, pneumonia, urinary tract infections, and catheter-related infections (21). *P. aeruginosa* and *A. baumannii* are among other common microorganisms that account for gram-negative infections in LT patients (7, 22). Outbreaks of S. maltophilia, Burkholderia cepacia, H. influenza and Campylobacter jejuni are also rarely reported (7). Gram-negative infections, including those caused by MDR Gram-negative bacilli (GNB), especially extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing gram-negative pathogens, have had an exponential rate in the last ten years, and have seriously affected patients after solid organ transplantation. (23) In this study, Gram-negative infections are the main cause (61.17%) of post-transplant infections. The most common types of Gram-negative bacteria in our cohort include *Klebsiella* and *E. coli*.

On the other hand, Gram-positive bacteria are among the pathogens that are increasingly dominant from clinical and economic point of view worldwide (24). Generally, catheter-related bloodstream infection , superficial and deep infections in the surgical site, bacteremia, and pneumonia can be caused by gram-positive bacteria.

Through the isolation of gram positive microorganisms Gram-positive cocci include Staphylococcus, Streptococci, and Enterococci are among the offending pathogens (7, 25). MRSA infection is a one of leading cause of infection among post transplantation hardships which lead to more mortality and morbidity rate (26). The prevalence rate of MRSA infection in Japan was 12.9%, Strategies that are suggested to effectively control and reduce MRSA infections include strict hand hygiene, postoperative skin disinfection, active monitoring of patients after transplantation, and daily bathing with chlorhexidine gluconate in the intensive care unit (27, 28).

The percentage of methicillin-resistant coagulase-negative staphylococci (MRCONS) in the other cohort studies was 42%. VRE colonization, which is associated with infections, affects different groups of patients, among which liver recipients were the most common affected group (23). In contrast, the frequency of VRE in the study population was only 1.94%. The rate of VRE infection is highly variable and center-specific; for example, according to pervious USA study, it was estimated to be 4.91% (7, 28, 29). The incidence of vancomycin-resistant enterococcal (VRE) infections lessen between the years of 2012 up to 2017 (30, 31). The low frequency of VRE in our study compared to other similar investigations can be attributed to the development and implementation of antibiotic stewardship programs under the supervision of an infectious specialist and a clinical pharmacist in Bu Ali Sina hospital in recent years, which has led to a significant reduction in inappropriate use of broad-spectrum antibiotics such as vancomycin. Although there is still a need for trained personnel and providing a tool for therapeutic monitoring of drugs such as vancomycin and determining its appropriate dosage, and the availability of clinical pharmacist services in hospitals to assess the pattern of antibiotic use (32).

In this study, the most gram-positive pathogen isolated mainly includes staphylococci and enterococci, which is consistent with the above studies.

There are some limitations in the present study: First, only bacterial infections were examined and other infections such as viral and fungal were not assessed, Second, only early bacterial infections during hospital stay after LT were considered. Finally, there was lack of detailed information about the isolated pathogens, including the investigation of the genetic patterns of resistance and the determination of MIC value for MDR and XDR bacterial species, as well as the lack of access to some antibiotics' sensitivity in our medical centers, such as tigecycline, ceftazidime, and avibactam.

5. Conclusion

Adult LT recipients are at risk of post-transplant bacterial infections, which can cause several complications. A high prevalence of bacterial infection was observed in our hospitalized patients in the first month after LT. Also, urinary tract infection was the most common type of infection after transplantation in adult liver transplant recipients, and length of stay in ICU, length of hospital stay, length of mechanical ventilation are among the risk factors affecting bacterial infection after LT. By knowing the risk factors of contracting these infections and eliminating the risk factors, we can take steps to reduce the number of infections.

Conflict of Interest

The authors declare no conflict of interest.

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