ORIGINAL RESEARCH

Comparison of Ceftizoxime Plus Ampicillin-Sulbactam versus Gentamicin Plus Ampicillin-Sulbactam in the Prevention of Post-Transplant Early Bacterial Infections in Liver Transplant Recipients: A Randomized Controlled Trial

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Purpose: In this study, we aimed to compare the efficacy of combined ceftizoxime with ampicillin-sulbactam versus combined gentamicin with ampicillin-sulbactam as prophylactic antibiotic regimen in preventing early bacterial PTIs in liver TX recipients at a referral center.

Patients and methods: All patients older than 18 years who had undergone liver TX at Abu-Ali Sina transplantation center in Shiraz, Iran from July 2018 to April 2019 were included in this study. In a single-blinded manner, the participants randomly received either combined intravenous ceftizoxime plus ampicillin-sulbactam (ceftizoxime group) or gentamicin plus ampicillin-sulbactam (gentamicin group) as prophylactic antibiotic regimen before the incision of the surgery, which was continued for 48 hrs after liver Tx. The rate and type of bacterial infections, length of hospital and intensive care unit (ICU) stay, mortality rate, and kidney function were assessed during 1 month following liver TX in the two groups.

Results: Two hundred and thirty patients were divided into two groups. One patient in the gentamicin group and five in the ceftizoxime group were excluded due to emergency exploratory laparotomy within the first 3 days after transplantation. The rate of bacterial infections during the first month after transplantation was 25.4%. This rate was significantly lower in the gentamicin group (13.16%) in comparison to the ceftizoxime group (38.18%) (*P value*<0.01), based on the univariate logistic regression analysis. Length of ICU and hospital stay and also mortality rate were significantly lower in the gentamicin group (*P value* <0.01). There was no significant difference regarding kidney function between the two groups (*P value* = 0.16).

Conclusion: Our results suggested that gentamicin can be considered as a promising agent in prophylactic antibiotic regimen for patients undergoing liver TX.

Trial registration: The study was registered at the Iranian Registry of Clinical Trials (IRCT20120731010453N2; http://www.irct.ir/).

Keywords: liver transplantation, antibiotic prophylaxis, infection, acute kidney injury

Introduction

Liver transplantation is one of the ways to cure end-stage liver diseases.[1] Over the past decade, the survival rate of liver transplant recipients has improved. This is mainly due to advances in surgical techniques, the introduction of new immunosuppressive agents

and the upgrading of diagnostic methods for early detection and prevention of infections.[2] A study by Nickeghbalian et al. estimated that the one-year survival of liver transplant recipients was 91%.[3]

One of the most important causes of mortality and morbidity after transplantation is post-transplant infections (PTIs).[4,5] In several studies, the incidence of PTIs was reported to be more than 50%.[5] The mortality rate was reported 24–36% in bacteremic recipients.[6] Bacterial, fungal and viral agents are the most important pathogens of PTIs, respectively.[6,7] The most important risk factor of PTIs is immunosuppression state. Other risk factors are the model for end-stage liver disease (MELD) score of more than 30 before transplantation, reoperation after transplantation, need to renal replacement therapy and more than 48 hrs of admission in the intensive care unit (ICU).[7,8]

In many studies, the occurrence of PTIs were classified into three periods: early (during the first 30 days after transplantation), intermediate (between the 1st and 6th month after transplantation), and late (6 months after transplantation).[9] Early period PTIs are mainly due to nosocomial bacterial infections. Surgical site infections (SSIs), pneumonia, bacteremia, and urinary tract infection were reported as the most common site of infections in the early period.[10] Preventing PTIs are important because of its effect on the transplantation failure rate.

Prophylactic antimicrobial therapy is frequently used in the early post-transplant period to reduce the incidence of PTIs. Third-generation cephalosporins, carbapenems, aminoglycosides, beta-lactams-beta-lactamase inhibitors and fluoroquinolones are being used alone or in combination with each other to prevent bacterial PTIs.[11] It is of great importance to select the prophylactic antibiotic regimen based on common infections, local guidelines and physician preferences in each center.

Due to the importance of selecting an appropriate prophylactic antibiotic regimen, we conducted this clinical trial to compare the efficacy of combined ceftizoxime with ampicillin-sulbactam, which is being used at our center versus combined gentamicin with ampicillin-sulbactam to prevent early bacterial PTIs in liver transplant recipients.

Materials and Methods
Trial Design
This is a randomized, single-blinded, clinical trial study with parallel design. Participants were assigned to either intervention or control groups (1:1 allocation ratio) based on blocked randomization method. Eligible patients were recruited from July 2018 to April 2019 at the Abu-Ali Sina transplantation hospital in Shiraz, Iran. The rate of bacterial PTIs was recorded and compared between the two groups within the first 30 days after transplantation.

The protocol and patient informed consent form were reviewed and approved by the local Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS. REC.1397.644). The study was registered at the Iranian Registry of Clinical Trials (IRCT201120731010453N2; http://www.irct.ir/). Participation in this study was completely voluntary. The study was carried out in accordance with the principles of the Declaration of Helsinki. The purpose of the study was explained for patients prior to their enrollment. All participants signed the written informed consent prior to their participation. Patients were free to withdraw from the study at any time.

Study Participants
Based on the data from previously published studies[12] and with a study power of 1- β=0.8 and α=0.05, and 1:1 allocation ratio between the treatment and control groups, the sample size was calculated to be at least 91 patients per group.

All patients older than 18 years who had undergone liver transplantation surgery were included in this study. Patients were excluded from the study if any of the following conditions existed: 1) use of antibiotics during their current hospital stay; 2) history of any infection before liver transplantation; 3) death earlier than 3 days after liver transplantation; 4) pregnant and lactating women; 5) history of sensitivity to one of the antibiotics used in this study; and 6) simultaneous liver-kidney transplantation.

All patients were transferred to the intensive transplant unit (ITU) after liver transplantation and visited daily by transplant surgeon, gastroenterohepatologist, and an infectious disease specialist. The patients' demographic, clinical and laboratory data were recorded. In each visit, the clinical and paraclinical changes were assessed and they were asked about any potential side effects.

Intervention
Participants either received combination of intravenous ceftizoxime (2 g every 8 hrs) with ampicillin-sulbactam (3 g every 6 hrs) or combination of gentamicin (5 mg/kg every 24 hrs for two single doses) with ampicillin-sulbactam (3 g every 6 hrs) as prophylactic antibiotic regimen. In both groups, antibiotics were infused intravenously 1 hr before the surgery and continued for 48 hrs

after liver transplantation through central venous catheter. The dose of antibiotics was adjusted based on the patient's glomerular filtration rate (GFR), if needed.

To prevent fungal infections, fluconazole (100 mg twice per day) was prescribed for all patients for 30 days. Trimethoprim/sulfamethoxazole (480 mg daily) was prescribed for 1 year as prophylaxis for pneumonia caused by *Pneumocystis jirovecii* (PJP). Also, intravenous ganciclovir (5 mg/kg/day) or oral valganciclovir (900 mg per day) was prescribed to prevent cytomegalovirus infection in seropositive patients. Hepatitis B immunoglobulin, along with antiviral drugs such as tenofovir or lamivudine, was administered after liver transplantation if the indication of liver transplant was hepatitis B virus infection.

Combinations of tacrolimus or cyclosporine with low dose prednisolone (20 to 10 mg per day) were used as primary standard immunosuppressive agents after induction therapy in all patients. To suppress acute rejection episodes, high dose of intravenous methylprednisolone (1 to 3 g daily for 3 consecutive days) and higher dose of tacrolimus were used. Plasma tacrolimus and cyclosporine levels were monitored closely.

Primary and Secondary Outcomes

The primary outcome was to evaluate the effectiveness of the two different prophylactic antibiotic regimens in preventing PTIs during the first month after liver transplantation. Secondary outcome measures included mortality and acute rejection rates, ICU and hospital length of stay, and the need for renal replacement therapy.

Biochemical Analysis for Evaluation of Renal Function

Plasma creatinine and blood urea nitrogen (BUN) levels were measured daily in all patients. Kidney function was assessed by calculating GFR. The trend of GFR was monitored using RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria in all patients[13] (Table 1).

Also, to assess the occurrence of acute tubular necrosis (ATN), fractional excretion of sodium (FENa) was calculated based on serum and urine levels of creatinine and sodium in days 0 (baseline) and 7. FENa more than 2% were considered as ATN. Aminoglycoside nephrotoxicity was defined as either increasing more than 0.5 to 1 mg/dL (44 to 88 µmol/L) or 50% in plasma creatinine concentration from the baseline value.[14]

Microbiological Study

Based on clinical and laboratory findings, microbiological surveillance cultures such as blood, urine, sputum, and abdominal fluid were performed. Chest X-ray was obtained in patients who were suspicious to pneumonia.

Blood culture was obtained by standard procedure. The automats used were the BacT/ALERT 3D-automated blood culture system (bioMérieux, Durham, NC, USA) and the BACTEC FX (BDDiagnostic Systems, Sparks, MD, USA) (FX) for rapid microbial detection.

Results were interpreted according to the clinical and laboratory standards institute (CLSI) guideline.[15] An expert infectious disease specialist exploited clinical guidelines of the centers for disease control (CDC) for diagnosis of PTIs.[16]

Statistical Analysis

The analysis was conducted using SPSS 25 software (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed by frequency and percentage. Normal distribution of data was calculated, using Shapiro–Wilk test. Normally distributed continuous variables were reported as mean (± SD). Non-normally distributed continuous data were expressed as median (interquartile range). Chi-square or Fisher exact test was used to evaluate possible associations among categorical variables, if appropriate. Parametric and non-parametric continuous variables were analyzed using independent *t*-test and Mann–Whitney tests, respectively. Multivariate stepwise logistic regression was used to calculate odds ratio (OR) and

Table 1 Classifications of Kidney Function According to RIFFLE Criteria

Stage	GFR Criteria	Urine Output Criteria
Risk	Increased serum creatinine 1.5 times or GFR decrease >25%	<5 mL/kg/h for 6 h
Injury	Increased serum creatinine 2 times or GFR decrease > 50%	<5 mL/kg/h for 12 h
Failure	Increased serum creatinine 3 times or GFR decrease > 75% or serum creatinine > 4 mg/dL	<3 mL/kg/h for 24 h or anuria for 12 h
Loss	Complete loss of kidney function > 4 weeks	
ESKD	End stage kidney disease (> 3 months)	

Abbreviation: GFR, glomerular filtration rate.

their 95% confidence interval (CI) to assess the possible risk factors of PTIs and gentamicin nephrotoxicity. For this purpose, various demographic, clinical, and paraclinical characteristics of patients were considered as independent variables and entered into the primarily univariate model separately. Those with P values less than 0.05 were then selected and entered into the final multivariate model. Comparison of the mean values of serum creatinine within and between the two groups in the first 10 days was done, using one-way analysis of variance (ANOVA) with repeated measures. P values less than 0.05 were considered to be statistically significant.

Results

After screening 253 patients, 230 of them were divided into two groups (115 patients each). One patient in the gentamicin plus ampicillin-sulbactam group (gentamicin group) and five patients in the ceftizoxime plus ampicillin-sulbactam group (ceftizoxime group) were excluded due to emergency exploratory laparotomy within the first 3 days after transplantation (Figure 1).

Patients' demographic and baseline laboratory data are shown in Table 2.

The rate of PTIs during the first month after transplantation was 25.4%. According to univariate logistic regression analyses, this rate was significantly lower in the gentamicin group (13.16%) in comparison with the ceftizoxime group (38.18%) (OR = 0.245, 95% CI: 0.126–0.477; P value <0.001). However, after adjusting our intervention for independent variables with probable confounding effects in the multivariate logistic regression

analysis, only the length of hospital stay was significantly associated with PTIs (OR = 0.782, 95% CI: 0.704–0.868; P value <0.001) (Table 3).

The results of clinic-related outcomes are presented in Table 4. Apart from the rates of bacterial infection, the length of hospital stay (P value <0.001), length of ICU stay (P value <0.001), and mortality rate (P value <0.001) were also lower in the gentamicin group than those in the ceftizoxime group. In contrast, the mean onset for bacterial infection after liver transplantation was comparable between the two groups (P value = 0.08).

The number of isolated pathogens during the first month after transplantation was poly-microbial (n=15), *Klebsiella sp.* (n=7), *Escherichia coli* (n=6), methicillin-resistant *Staphylococcus aureus* (MRSA) (n=2), vancomycin-resistant *Enterococci* (VRE) (n=2), and *Pseudomonas sp.* (n=1). There was no statistically significant difference in the type of pathogens between the two groups (P value = 0.11).

Seven isolated Enterobacteriaceae were extensively drug-resistant (XDR) and 17 were multi-drug-resistant (MDR). The number of MDR pathogens in the gentamicin group was significantly lower (P value=0.04), but there was no significant difference in the number of XDR pathogens (P value=0.68) between the two groups.

Conversely, the sites (types) of infection differed significantly between the two groups (P value <0.001). For example, ventilator-associated pneumonia was more common in the ceftizoxime than the gentamicin group (54.76% and 20%).

Based on the definition of aminoglycoside nephrotoxicity, 8% of the patients in the gentamicin plus ampicillin-sulbactam group developed ATN. Different aspects and indexes of renal function in the two groups are shown in Table 5. GFR 1 week after transplantation, ATN episodes, number of patients requiring hemodialysis or continuous renal replacement therapies (CRRT), and rate of ATN based on the RIFLE criteria were comparable between the ceftizoxime and gentamicin groups.

According to Figure 2, the mean changes of serum creatinine level during the first 10 days after liver transplantation did not differ significantly either within or between ceftizoxime and gentamicin groups.

Comparison of different demographic, clinical and paraclinical characteristics between patients with and without ATN after transplantation are listed in Table 6. According to univariate analysis, gender (P value = 0.016), length of ICU stay (P value = 0.004), length of hospital stay (P value = 0.010), bacterial infection after transplant (P value = 0.002),
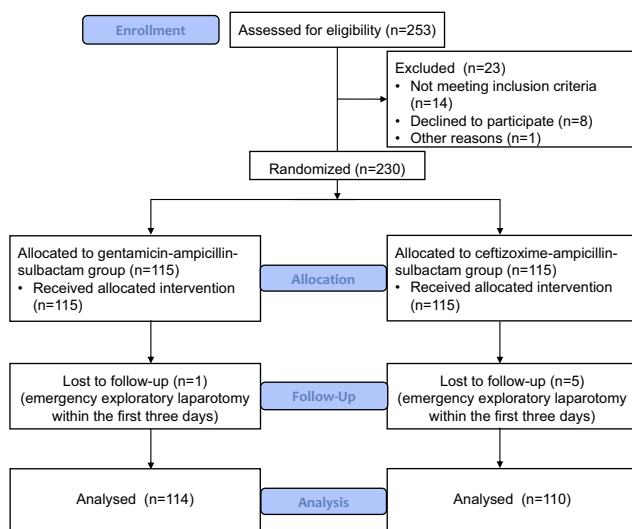

Figure 1 CONSORT diagram of the participants.

Table 2 Baseline Demographic, Clinical and Laboratory Data of Patients Between Ceftizoxime and Gentamicin Groups

Variable		Gentamicin Group (n=114)	Ceftizoxime Group (n=110)	*P*value
Age (year) (mean±SD)		43.92±12.92	44.72±13.43	0.56
Gender (N, %)	Male	76 (66.6)	68 (61.81)	0.53
	Female	38 (33.33)	42 (38.18)	
BMI (kg/m^2)		22.69±3.50	23.85±4.51	0.21
MELD Score		17.53±5.85	19.67±7.21	0.22
Length of operation (minute)		303.62±63.00	290.41±78.02	0.19
Indication for transplantation (N)	Hepatitis B virus	13	18	0.16
	Primary sclerosing cholangitis	36	14	
	Cryptogenic cirrhosis	13	19	
	Wilson disease	5	4	
	Hepatocellular carcinoma	6	4	
	Autoimmune hepatitis	13	27	
	Nonalcoholic steatohepatitis	11	9	
	Hepatitis C virus	6	4	
	Alcoholic liver disease	0	3	
	Others	7	7	
Albumin before transplantation (mg/dl)		2.56±0.56	2.53±0.59	0.99
WBC before transplantation (10^9/L)		10.01±5.07	9.71±5.96	0.21
Biliary anastomosis(%)	Choledochocholedochostomy	86(75.44)	71(64.55)	0.23
	Choledochojejunostomy	28(24.56)	39(35.45)	
Comorbid disease(N)	Diabetes mellitus	17	7	0.16
	Hypertension	1	2	
	Asthma	2	4	
	Duodenal ulcer/gastric ulcer	3	0	
	DVT	2	2	

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease; WBC, white blood cells; DVT, deep vein thrombosis.

type of prophylactic antibiotic regimen (P value = 0.019), reoperation (P value = 0.005), mechanical ventilation more than 4 hrs after transplantation (P value = 0.001), use of nephrotoxic agent(s) (P value = 0.024), hemoglobin level before transplant (P value = 0.047), total (P value = 0.003) as well as direct (P value = 0.003) bilirubin level before transplant, and ALT level before transplant (P value < 0.001) were selected. However, only ALT level before transplant (OR = 1.001, 95% CI: 1.000–1.001; P value = 0.005) was significantly associated with ATN after transplantation based on the multivariate analysis.

Discussion

PTIs are the most important cause of mortality and morbidity after liver transplantation. One of the most important strategies used to reduce PTIs is rational and appropriate use of prophylactic antibiotic regimen.[17] In this clinical trial, the combination of gentamicin and ampicillin-sulbactam was compared with the routine antibacterial prophylactic regimen in our center (ceftizoxime and ampicillin-sulbactam). The clinical effectiveness of gentamicin plus ampicillin-sulbactam in preventing PTIs was significantly higher based on univariate analysis and its renal safety was comparable with the ceftizoxime plus ampicillin-sulbactam regimen.

In our study, the rate of PTIs during the first month after transplantation was 25.4%. Previous studies reported a wide range of PTIs incidence. In the study by Kim et al., the rate of PTIs in the first month after transplantation was 30.2%.[10] In other studies, the rate of PTIs was reported from 14.1% to 75%.[7] The difference in choosing the prophylactic antibiotic regimen, length of follow up, design of the study, different microbiological environments, and difference in the definition of PTIs are the factors that might lead to such a wide range of variation.

Table 3 Comparison of Different Demographic, Clinical and Para Clinical Characteristics Between Patients with and Without Early Bacterial Infection After Liver Transplantation

Parameter	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.995 (0.972–1.018)	0.668	–	–
Gender	0.629 (0.340–1.162)	0.139	–	–
BMI	0.924 (0.845–1.011)	0.08	–	–
MELD score	0.934 (0.891–0.980)	0.005	0.940 (0.876–1.009)	0.086
ICU length of stay	0.814 (0.748–0.886)	<0.001	0.948 (0.832–1.080)	0.422
Hospital length of stay	0.778 (0.716–0.845)	<0.001	0.782 (0.704–0.868)	<0.001
Underlying disease	0.963 (0.860–1.078)	0.512	–	–
Type of surgery	0.763 (0.335–1.737)	0.519	–	–
Biliary anastomosis	1.319 (0.533–3.261)	0.549	–	–
Length of operation	0.997 (0.750–1.326)	0.986	–	–
Reoperation	8.626 (2,90–25.5)	<0.001	3.056 (0.477–19.573)	0.238
History of antibiotic therapy within 1 week before transplantation	1.859 (0.957–3.60)	0.068	–	–
History of hospitalization within 3 months before transplantation	1.973 (1.031–3.776)	0.040	1.439 (0.530–3.904)	0.475
Mechanical ventilation more than 48 hr after transplantation	32.329 (10.520–99.345)	<0.001	–	–
WBC before transplantation	0.989 (0.937–1.044)	0.688	–	–
Type of prophylactic antibacterial regimen	0.245 (0.126–0.477)	<0.001	0.619 (0.244–1.571)	0.313

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease; ICU, intensive care unit.

Table 4 Comparison of Clinical Outcome Between Ceftizoxime and Gentamicin Groups

Variables			Gentamicin Group	Ceftizoxime Group	*P*value
Bacterial infection(%)			15 (13.16)	42 (38.18)	<0.01
Length of ICU stay (days)			7.84±3.56	11.25±11.43	<0.001
Length of hospital stay (days)			13.22±4.80	17.48±11.14	<0.001
Mortality (N)			3	16	<0.001
Rejection episodes(N)			6	3	0.33
Type of infections (N)	VAP		3	22	<0.001
	Urinary tract infection		5	3	
	Surgical site infection		2	3	
	Bloodstream infection		1	2	
	Co-infection	VAP+UTI	2	5	
		VAP+ Surgical site infection	1	4	
		VAP+ Bloodstream infection	1	1	
		Surgical site infection + Bloodstream infection	0	1	
Timing of infection after transplantation (day)			7.46±4.53	5.69±3.1	0.08
FK level (ng/mL)			5.46±4.23	5.24±4.34	0.34
VRE colonization (N)			21	18	0.1

Abbreviations: ICU, intensive care unit; VAP, ventilator-associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; FK, tacrolimus; UTI, urinary tract infection.

In recent years, Gram-negative bacteria have been considered as the most common cause of PTIs.[18] This becomes important due to the high rate of MDR among gram-negative bacteria.[19] One study in China reported that MDR gram-negative bacteria were isolated from 56% of PTIs cases.[7] In line with the aforementioned study, MDR

Table 5 Comparison of Different Renal Function Indexes Between Ceftizoxime and Gentamicin Groups

Variables		Gentamicin Group(N=114)	Ceftizoxime Group(N=110)	Pvalue
Baseline GFR (mL/min)		105.06±43.56	95.100±40.44	0.92
GFR one week after transplantation (mL/min)		104.10±37.85	92.75±49.35	0.16
Hemodialysis or CRRT (N)		12	14	0.23
Episodes of ATN (N)		23	18	0.38
RIFLE Criteria	Risk (N)	8	12	0.07
	Injury (N)	5	5	
	Failure (N)	8	10	
	Loss (N)	0	1	

Abbreviations: GFR, glomerular filtration rate; CRRT, continuous renal replacement therapies; ATN, acute tubular necrosis; FENa, fractional excretion of sodium.

gram-negative bacteria were the most common pathogens in our study. The rate of MDR pathogens in our study was about 55%, of which 48% were extended-spectrum beta-lactamases (ESBL). The number of MDR gram-negative isolates in the ceftizoxime group (N=12) was more than the gentamicin group (N=5).

Previous studies reported the prevalence of ESBL from 43.3% to 67%.[20,21] The increase in the rate of MDR and ESBL species not only increases the rate of mortality after liver transplant, but also leads to inefficiency of some antibiotic classes, such as cephalosporins, as part of the prophylactic antibiotic regimen.[22]

Some clinical guidelines have suggested the use of piper-acillin-tazobactam or the combination of ampicillin and ceftazidime 24 hrs or less prior to liver transplantation as

Figure 2 The mean changes of serum creatinine level during the first 10 days after liver transplantation.

prophylactic regimen.[11] A retrospective non-randomized study stated that the use of cephazolin alone could not prevent SSIs in post-transplant liver recipients.[23] Another single center study used ampicillin-sulbactam rather than cefazolin alone, but the author's concluded that ampicillin-sulbactam could not prevent SSIs.[24]

Although aminoglycosides has appropriate coverage against aerobic gram-negative bacilli, and has synergistic effect in combination with other antibiotics,[25] no study has compared the efficacy of gentamicin as a part of prophylactic antibiotic regimen in liver transplant recipients yet. Our rationale in selecting gentamicin plus ampicillin-sulbactam regimen in the current clinical trial was mainly based on both the reported frequency and pattern of pathogens causing PTIs in our center[26,27] (mostly, Acinetobacter spp. and Enterococci spp.) and also potential synergistic effects of aminoglycosides (e.g., gentamicin) in combination with beta lactams particularly against the MDR bacteria[25] (e.g., ampicillin-sulbactam).

Previous studies reported that the length of ICU and hospital stays, MELD score before transplantation, reoperation, and hospitalization within 3 months prior to the transplantation, administration of antibiotic 1 week before liver transplantation, and the type of biliary anastomosis are the risk factors for PTIs.[6,28] However, in the current study, only the length of hospital stay was significantly associated with PTI. Variations in the study setting, study population, methodology, and prophylactic antibacterial regimen should be taken into account for these differences.

Most of the PTIs risk factors are non-modifiable before the liver transplantation. Therefore, it is necessary to develop a proper prophylactic antibiotic regimen to prevent PTIs.
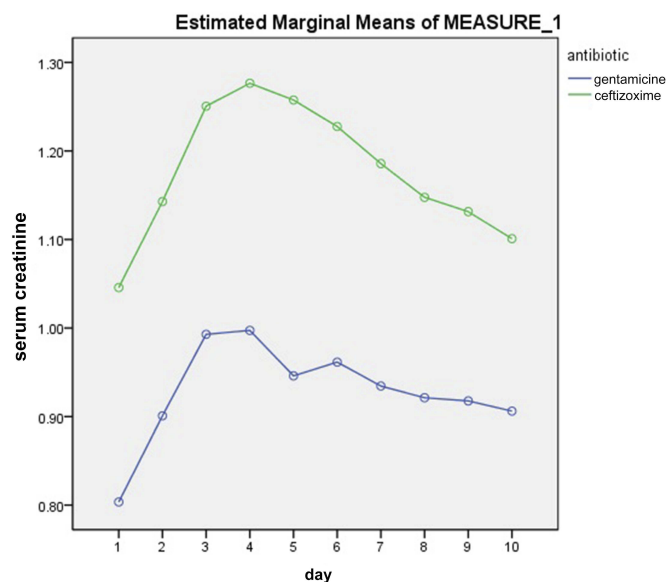
Table 6 Comparison of Different Demographic, Clinical and Para Clinical Characteristics Between Patients with and Without aminoglycoside nephrotoxicity After Liver Transplantation

Parameter	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.005 (0.980–1.031)	0.693	–	–
Sex	2.305 (1.170–4.538)	0.016	1.930 (0.825–4.515)	0.129
BMI	1.005 (0.909–1.111)	0.927	–	–
MELD score	0.980 (0.928–1.035)	0.468	–	–
Length of ICU stay	1.052 (1.017–1.088)	0.004	1.067 (0.975–1.167)	0.161
Length of hospital stay	1.044 (1.010–1.0078)	0.010	0.952 (0.873–1.038)	0.267
Bacterial infection after transplant	0.336 (0.167–0.679)	0.002	0.613 (0.179–2.093)	0.435
Underlying disease	1.082 (0.959–1.222)	0.201	–	–
Baseline GFR	1.002 (0.994–1.009)	0.618	–	–
FK level	1.016 (0.934–1.101)	0.712	–	–
Type of surgery	1.817 (0.758–4.358)	0.181	–	–
Biliary anastomosis	1.103 (0.414–2.944)	0.844	–	–
Length of operation	0.918 (0.666–1.256)	0.599	–	—
Reoperation	0.235 (0.086–647)	0.005	0.527 (0.117–2.366)	0.403
History of antibiotic therapy within 1 week before liver transplant	0.871 (0.467–1.838)	0.827	–	–
Mechanical ventilation more than 48 hr after transplantation	0.252 (0.109–0.584)	0.001	1.053 (0.263–4.217)	0.941
Rejection episodes	0.849 (0.170–4.240)	0.842	–	–
Concomitant use of nephrotoxic agent(s)	0.474 (0.247–0.907)	0.024	0.743 (0.250–2.208)	0.593
Level of hemoglobin before transplantation	0.811 (0.659–0.998)	0.047	0.809 (0.619–1.059)	0.123
Level of albumin before transplantation	0.709 (0.386–1.304)	0.269	–	–
Level of total bilirubin before transplantation	1.071 (1.024–1.120)	0.003	1.052 (0.925–1.195)	0.441
Level of direct bilirubin before transplantation	1.134 (1.044–1.232)	0.003	1.075 (0.844–1.371)	0.557
Level of ALT before transplantation	1.001 (1.000–1.001)	<0.001	1.001 (1.000–1.001)	0.005
Type of prophylactic antibacterial regimen	2.292 (1.145–4.587)	0.019	0.981 (0.402–2.391)	0.966

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease; ICU, intensive care unit; GFR, glomerular filtration rate; FK, tacrolimus; ALT, alanine transaminase.

A concern regarding the use of aminoglycosides is renal toxicity. It was estimated that renal toxicity was developed in 10–20% of patients who received aminoglycosides.[29] Based on the mentioned criteria for diagnosis of aminoglycosides renal toxicity, the rate of gentamicin nephrotoxicity was 8% in our study. Also, other aspects and indexes of renal function including GFR 1 week after transplantation, ATN episodes, number of patients requiring hemodialysis or CRRT, and the rate of ATN based on the RIFLE criteria did not differ significantly between the two groups. In other words, renal safety of our antibacterial prophylactic regimen was comparable with ceftizoxime plus ampicillin-sulbactam. This might be due to administration of gentamicin once daily and just for 48 hrs. Based on the results of various studies, administration of aminoglycosides with an interval of 24 hrs causes less renal toxicity, in addition to having the same antibacterial effects with shorter interval of administration.[30] Nielsen et al. investigated the effect of single dose of gentamicin on the rate of ATN in patients undergoing cardiac surgery,[31] and reported that the gentamicin group had more fluctuations in creatine levels during the first 72 hrs and most patients were within the first level of ATN according to RIFLE criteria. However, after the first 72 hrs, there was no difference in the level of creatinine among the patients. Also, there was no difference in the rate of hemodialysis between the two groups.

Our study had some limitations, and the first one was the fact that the patients were selected from a single center. Hence, it is necessary to conduct a multi-central study with a larger sample size to increase the external validity and statistical power of the study. Another limitation was the short duration of the follow-up. It is recommended that the effect of prophylactic antibiotic regimen should be investigated during at least 6 months. Also, it is suggested that the rate of non-bacterial infections after transplantation should be investigated.

Conclusion

According to the results of this study, gentamicin (5 mg/kg every 24 hrs) plus ampicillin-sulbactam (3 g every 6 hrs) regimen for 48 hrs compared to ceftizoxime (2 g every 8 hrs) plus ampicillin-sulbactam (3 g every 6 hrs)

significantly reduced the rate of PTIs during the first month after transplantation. In addition, our regimen led to lower ICU as well as hospital length of stay and also mortality rate. No significant difference was found between the two groups regarding different aspects of renal function. Therefore, it seems that gentamicin can be used safely as part of prophylactic antibiotic regimen in patients undergoing liver transplantation.

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Disclosure

The authors report no conflicts of interest in this work.

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