Bacterial Infections after Pediatric Liver Transplantation

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Abstract

Background: Liver transplantation (LT) is the only curative therapy for acute and chronic end-stage liver disease in pediatrics. Nevertheless, bacterial infection post-transplant account for one of the most significant causes of mortality which requires attention, along with appropriate antibacterial treatment. Therefor this study was designed to provide a multifaceted overview of bacterial infections during a one-year experience in the biggest pediatrics LT center in Iran.

Methods: In this retrospective cohort study, records from all liver transplant pediatrics in Abu-Ali Sina hospital, Shiraz, Fars, Iran from April 2019 to February 2020 were assessed. Demographic, laboratory, and clinical data were extracted along with the administered therapeutic approach for the patient.

Results: an incidence of 67.9% bacterial infection rate was observed, in which more than 64.06% of isolated pathogens were Gram-negative and 35.93% were gram-positive. The most isolated pathogens were *E. coli sp.* and *pseudomonas sp.* for gram negative, and *enterococci* and *staph sp.* for gram positive. Our study demonstrated that Intra-abdominal Surgical Site Infections (24.24%) was the most common site of infections in post LT pediatrics. According to the results of the sensitivity-resistance pattern of isolated pathogens, 24.39% of isolated gram-negative bacteria were Extensively drug resistant (XDR). Also, 30.43% of gram-positive bacteria were Vancomycin-resistant enterococci (VRE) and 8.69% of them were methicillin-resistant staphylococcus aureus (MRSA). Furthermore, multivariate regression analysis showed that the only risk factor for bacterial infections after LT is the length of stay in the ICU. The mortality rate in our study was 22%, which was significantly higher among the infection group (P = 0.008). Also, it was found that patients receiving colistin had a significantly shorter in length of stay in the ICU and hospital than those who did not receive colistin. There is no any significant difference between piperacillin-tazobactm versus meropenem as empirical treatment regarding clinical outcomes.

Conclusion: a high rate of bacterial infection was detected among hospitalized pediatrics in the early period after LT. High antibacterial resistance of bacteria isolated from LT pediatrics is alarming. Furthermore, Replacement of piperacillin-tazobactam instead of carbapenems in empirical treatment should be considered.

Background

Advances in medical science have increased the life expectancy of patients suffering from organ failure and end-stage disease. Patients with liver failure also fall into this category [1, 2]. One of the most effective treatment strategies for the survival of patients with advanced liver failure is liver transplantation (LT) [3, 4], especially in pediatrics in increasing their life expectancy. Indications for LT in pediatrics generally include cholestatic diseases, metabolic disorders, acute liver failure due to viral infections or drug use, chronic hepatitis, and malignancies [5].

Infections have obtained one of the most important causes of morbidity and mortality after solid organ transplants even compared to transplant rejection [6, 7]. The rate of infection after liver transplant varies

in different studies ranging from 21 to 47% among pediatrics [8–10].

The most frequent organism of post-transplant infection is usually bacterial (up to 70%), followed by viral and fungal [11, 12]. Bacterial infection in these patients may range from less severe infections, such as superficial wound infections, to severe, such as septic shock [8]. Various factors contribute to predisposing pediatrics liver transplant recipients to a greater risk for colonization and infection with multidrug-resistant organisms (MDRs), which include recurrent and prolonged hospitalizations, impairment of the immune system, and multiple uses of antibiotics [13]. Since there are significant developmental variations among pediatrics and adults that can considerably influence the pathophysiology and prognosis, caution is warranted in extrapolating the results of adult studies to pediatrics. Therefore, the evaluation of infection rates among pediatrics receiving LT is justified.

Therefore, this retrospective cohort study was designed to evaluate a multifaceted overview of bacterial infections during a one year experience which includes: incidence, type and susceptibility-resistance patterns of isolated pathogens, risk factors related to infections, as well as evaluation of different antibiotic regimens and their outcome in pediatrics candidate for LT in Shiraz organ transplant center, Abu-Ali Sina hospital as the only and biggest pediatrics LT center in Iran.

1. Method And Patients

1.1 Study design

In this retrospective cohort study, clinical and laboratory records from all liver transplant pediatrics under 18 years of age in Abu-Ali Sina hospital, Shiraz, Fars, Iran from April 2019 to February 2020 were assessed. This study was approved by the ethics committee of Shiraz University of Medical Sciences. All of the protocols were based on the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all the patients' parents or guardians.

1.2 Data Collection

The medical and laboratory records of all the patients were extracted from available electronic inpatient medical record databases in hospitals and reviewed by a pharmacist under the vision of clinical pharmacists. Demographic data such as age, gender, body mass index (BMI), etiology of end-stage liver disease, Pediatric End-Stage Liver Disease (PELD) score or the Model for End-Stage Liver Disease (MELD) score, and previous history of admission and antibiotic usage within one week to three months before of liver transplant were recorded. The technique of LT, the mean operation time, immunosuppressive regimens, and length of ICU and hospital stay, readmission, rejection or re-transplantation episodes, and clinical outcome after transplantation were also evaluated.

1.3 Infection Assessment

All patients in our center received antimicrobial prophylaxis consisting of ampicillin-sulbactam (150 mg/kg/day) and ceftizoxime (150 mg/kg/day till 72 hours after LT in all patients, except in those with biloenteric anastomosis (continued for 5 days). All pediatrics received trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis with 2-3 mg/kg TMP daily for the first 6 months after LT for prophylaxis of Pneumocystis jiroveci, fluconazole (3-5 mg/kg/day) for prophylaxis of fungal infection, and ganciclovir (10 mg/kg/day) or valganciclovir (13 mg/kg/day) for prophylaxis of cytomegalovirus infection that was commenced and continued for at least one month after LT. [14].

Also, as a suppressive regimens, a combination of tacrolimus, prednisolone, and mycophenolate mofetil are prescribed and according to the condition of the transplanted graft, and also based on the plasma levels and the duration since the time of transplant, doses will be adjusted.

All the patients were visited and evaluated daily by a transplant surgeon, pediatric gastroenterohepatologist, and a subspecialist of pediatric infectious diseases after transplantation.

If an infection is suspected, the necessary work-up in this area will be conducted, including chest and abdominal radiography, inflammatory factors such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, complete blood count (CBC) blood culture samples (central and peripheral), urine and sputum culture, and in case of presence of any drains, samples will be obtained and sent for analysis. Then, at the discretion of the pediatric infectious disease specialist and based on the patient's clinical condition, a combination of vancomycin or clindamycin for empirical coverage of gram-positive pathogens with additional antibiotics covering gram-negative bacteria such as carbapenems, betalactam-betalactamase inhibitor or Fluoroquinolones and, if necessary, an antifungal is used and after determining the type of pathogen isolated, definitive therapy is performed.

In this study, the classification type of infections was based on the CDC/NHSN surveillance classification of healthcare-associated infection and criteria for specific types of infections in the acute care setting [15]. sepsis diagnosis is based on Surviving sepsis campaign [16] and Intra-abdominal infection includes peritonitis, Cholangitis, abdominal abscess, and Infected hepatic necrosis based on pathological and radiographic findings.

Following data were recorded for each episode of infection: sign and symptoms, date of the event according to CDC definition, site of infection, isolated organism and its antimicrobial susceptibility pattern (which performed by using Kirby-Bauer disc diffusion method and according to CLSI guideline), type and length of antibacterial usage and clinical outcome of infections. Multidrug-resistant (MDR) and Extensive Drug Resistance (XDR) pathogens were defined in accordance with the Consensus Statement of the European Centre for Disease Prevention and Control and the American CDC evidence of infection [14].

1.4 Statistical Analysis

All the statistical analyses were performed by statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 26.0. Descriptive statistics were presented as mean ± SD and proportions as appropriate. Factors affecting the difference between the infected and non-infected group was done by using a binary logistic regression model and multivariate analyses. The Chi-square test or Fisher's exact test was used to compare categorical data. The statistical tests used in the univariate analysis were Student's t-test and Mann-Whitney U test. Covariates significant ($P < 0.05$) in the univariate model were included in the multivariable linear regression. The possible association between different demographic, clinical, and paraclinical characteristics of the study population and the development of infection was assessed by the multivariate logistic regression analysis. In the first step, each independent variable entered into the univariate model. In the following, those with $P < 0.05$ in the univariate model were selected and entered into the final multivariable regression model. Comparison of the effect of different empirical antibiotic regimens on white blood cells, body temperature, and CRP levels at consecutive days after starting antibiotic therapy was done by using a one-way analysis of variance (ANOVA) with repeated measures. The statistical significance level was set at $p < 0.05$.

2. Results

Over the period of this study, 84 patients had undergone LTs in our center in which four were excluded due to incomplete clinical records. Among the 80 enrolled pediatrics, the median age was 60 months (mean: 72.18 ± 48.48; range from 8 to 204 months), with a 52 (65%) male to 28 (35%) female rate. Table 1 demonstrates the demographic and clinical related data of these patients with a comparison between the infected and non-infected group.

Table 1
Demographic and clinical variables of pediatric liver transplant patients among the infected and non-infected group (N = 80)

Variables	**Total (mean ± SD) or (%)** ***n = 80***	**Groups (mean ± SD) or (%)**		
		Infected ***n = 55***	**Non-infected** ***n = 25***	**p-value**
Age (months)	72.18 ± 48.48	70.18 ± 4971	88.40 ± 42.18	0. 42
Gender				
Male	52 (65%)	35 (67.3)	17 (32.7)	0.96
Female	28 (35%)	19 (67.9%)	9 (32.1)	
BMI (kg/m^2)	18.00 ± 3.68	18.05 ± 3.81	17.88 ± 3.47	0.43
Exploration surgery after Tx				
Yes	27 (33.8%)	20 (74.1)	7 (25.9)	0.37
No	53 (66.2%)	34 (64.2)	19 (35.8)	
Rejection				
Yes	22 (27.5)	17 (77.3)	5 (22.7)	0.25
No	58 (72.5)	37 (63.8)	21 (36.2)	
Underlying Liver Dx				
PFIC	13 (16.3)	11 (84.6)	2 (15.4)	0.08
Crigler Najjar	6 (7.5)	3 (50)	3 (50)	
Biliary atresia	12 (15)	11 (91.7)	1 (8.3)	
Cryptogenic	7 (8.8)	5 (71.4)	2 (28.6)	
Wilson Disease	15 (18.8)	8 (53.3)	7 (46.7)	
Others	26 (32.5)	15 (57.7)	11 (42.3)	

Variables	Total (mean ± SD) or (%) *n = 80*	Groups (mean ± SD) or (%)		
		Infected *n = 55*	Non-infected *n = 25*	p-value
Type of Anastomoses				
Duct to duct	57 (72.2)	37 (64.9)	20 (35.1)	0.50
Roux-en-Y hepaticojejunostomy	22 (27.5)	16 (72.7)	6 (27.3)	
Type of Surgery				
Piggy Back	72 (91.1)	49 (68.1)	23 (31.9)	0.56
Standard	7 (8.9)	4 (57.1)	3 (42.9)	
Re-transplantation	3 (3.89)	2 (3.84)	1 (4)	0.975
PELD score	20	21.52 ± 9.37	20.63 ± 13.3	0.762
MELD score	19.5	18 ± 1.41	25 ± 7.07	0.997
CMV Infection	6	4	2	0.999
Length of Hospital Stay	24.01 ± 16.99	27.18 ± 18.69	17.42 ± 10.24	0.022
Length of ICU Stay	22.75 ± 15.87	26.62 ± 17.62	14.69 ± 6.11	0.003
Length of mechanical ventilation after Tx	3.14 ± 2.39	3.88 ± 3.07	1.88 ± 0.77	0.016
Length of operation (minutes)	269 ± 60.15	274 ± 59.63	258 ± 60.79	0.245
Re-hospitalization after Tx	19	18	1	0.017
Tacrolimus Level(ng/dl)	10.33 ± 4.34	10.75 ± 4.20	9.36 ± 4.5	0.204
Positive History of Antibiotics usage in the past week before Tx	27 (33.75)	19 (70.37)	8 (29.63)	0.696
Positive History of Hospitalization in the past three months prior Tx	21 (26.25)	13 (61.9)	8 (39.1)	0.525
Immune suppressive regimen				
Tacrolimus + prednisolone	30 (78.94)	21 (70)	9 (30)	0.428

Variables	Total (mean ± SD) or (%) *n = 80*	Groups (mean ± SD) or (%)		
		Infected *n = 55*	Non-infected *n = 25*	p-value
Tacrolimus + prednisolone + cellcept	38 (47.5)	12 (31.57)	26 (68.42)	
Cellcept + Prednisolone	30 (38)	11	19	
Prednisolone	1 (1.3)	1	0	
Cellcelpt + Prednisolone + Cyclosporin	1 (1.3)	1	0	
WBC count on admission date	9.03 ± 4.25	8.73 ± 4.09	9.96 ± 4.59	0.372
WBC count after one week	10.32 ± 5.79	10.37 ± 5.47	10.18 ± 6.61	0.898
Positive Stool VRE	16 (25)	13 (31.7)	3 (13.04)	0.199
Expire	18 (22.5)	10 (55.55)	8 (44.44)	0.008

Notes:

Abbreviations: BMI: Body mass index; PFIC: Progressive Familial Intrahepatic Cholestasis; PELD: Pediatric End-Stage Liver Disease; MELD: Model for End-Stage Liver Disease; Tx: Transplant; Dx: Disease; CMV: Cytomegalovirus; ICU: Intensive care unit; WBC: white blood cell; VRE: Vancomycin-resistant Enterococcus; SD: Standard deviation

The results of this study showed that 55 patients (67.9%) had at least one bacterial infection in one year after transplantation. The mean timing of infections after LT was 7.87 ± 3.32 days. Intra-abdominal Surgical Site Infections (24.24%), Co-infections (19.69%), urinary tract infection (UTI) (19.69%), and bloodstream infections (19.69%) were the most common types of infections reported in these patients, respectively. Table 2 shows the frequency of bacterial infections based on the site of infection and the type of isolated pathogens. More than 64.06% of the isolated pathogens were Gram-negative and 35.93% were gram-positive. The most isolated pathogens were *E. coli sp.* (n = 19), *enterococci* (n = 9), *Staphylococcus sp.* (n = 8), and *pseudomonas sp.* (n = 7), *Streptococcus spp* (n = 6), *Klebsiella sp.* (n = 6), *Acinetobacter sp.* (n = 4), *Enterobacter sp.* and *Proteus Mirabilis sp.* (n = 2), and *Citrobacter* (n = 1). According to the results of the sensitivity-resistance pattern of isolated pathogens, 24.39% of the isolated gram-negative bacteria were Extensively drug-resistant (XDR) and 12.19% of them were of Extended-spectrum beta-lactamase (ESBL) type. Also, 30.43% of the gram-positive bacteria were Vancomycin-resistant enterococci (VRE) and 8.69% of them were methicillin-resistant Staphylococcus aureus (MRSA). Furthermore, the most frequent site for isolated XDR pathogens was the abdomen, while the most frequent one for MDR was the urinary tract.

Table 2
Site of infections and isolated bacterial pathogens amongst pediatrics who had undergone liver transplantation (N = 80);

Type of infection and isolated pathogen	Frequency (%)
UTI	13 (19.69)
E. coli	6 (46.15)
Staphylococcus coagulase-negative	1 (7.69)
Klebsiella	1 (7.69)
Enterobacter	1 (7.69)
E. coli + Citrobacter	1 (7.69)
E. coli + Proteus mirabilis	1 (7.69)
E. coli + staphylococcus coagulase-negative	1 (7.69)
E. coli + enterococcus	1 (7.69)
Bloodstream infection	13 (19.69)
E. coli	3 (23.08)
Staphylococcus coagulase-negative	1 (7.69)
Enterococcus spp.	6 (46.15)
Streptococcus + pseudomonas	1 (7.69)
Staphylococcus epidermis + Streptococcus	1 (7.69)
Gram-negative bacilli	1 (7.69)
VAP	3 (4.54)
E. coli	1 (33.33)
Acinetobacter	1 (33.33)
Staphylococcus coagulase-negative	1 (33.33)
Sepsis (Primary or secondary)	4 (6.06)
Pseudomonas	1 (25)
streptococcus sp.	1 (25)
enterococcus sp.	1 (25)
Klebsiella	1 (25)
Gastroenteritis	4 (6.06)

Type of infection and isolated pathogen	Frequency (%)
Intra-abdominal Surgical Site Infection	16 (24.24)
E. coli	2 (18.75)
Pseudomonas	4 (37.5)
streptococcus Spp.	2 (18.75)
Klebsiella	1 (6.25)
staphylococcus epidermis	1 (6.25)
Streptococcus + pseudomonas	1 (6.25)
Acinetobacter	2 (18.75)
E. coli + Klebsiella + enterococcus + proteus mirabelis	1 (6.25)
E. coli + Klebsiella + Enterobacter	1 (6.25)
Acinetobacter + Klebsiella	1 (6.25)
Coinfection	13(19.69)
GE + VAP	1 (7.69)
surgical site infections + BSI (blood stream infections)	4 (30.77)
VAP + BSI	2 (15.38)
UTI + surgical site infections	3 (23.08)
BSI + surgical site infections + VAP	2 (15.38)
UTI + VAP	1 (7.69)
Notes: **Abbreviations**: UTI: Urinary tract infection; E. coli: Escherichia coli; VAP: Ventilator-associated pneumonia; GE: Gastroenteritis; BSI: Bloodstream infection	

Our results, as demonstrated in Table 1, showed that the length of stay in ICU and hospital, length of mechanical ventilation after transplant, re-hospitalization and mortality rate were significantly higher in the group of infected than in non-infected pediatrics.

After assessing the quantitative and qualitative variables and their relationship with infection, multivariate regression analysis showed that the only risk factor for bacterial infections after LT was the length of stay in the ICU (Table 3).

Table 3
Multivariate linear regression of the association between qualitative and quantitative variables and infection rate among pediatric liver transplant patients (N = 80)

Variable	OR	95% CI	P-value
Age	1.009	0.996–1.021	0.176
Length of ICU stay	0.687	0.506–0.933	0.016
Length of Hospital stay	1.232	0.948–1.601	0.118
Length of mechanical ventilation	1.211	1.00–1.519	0.124
Re-hospitalization	5.377	0.947–30.525	0.058
Re-transplantation	1.982	0.876–1.664	0.078
Vascular anastomotic stenosis	2.221	0.678–1.113	0.066

Table 4 demonstrates the frequency of antibiotic use in empirical and definitive conditions along with the average duration of administration during the study period. Evaluation of antibiotics prescribed revealed that 57.1% of empirical regimens included Vancomycin with carbapenems (mainly meropenem), 30% included vancomycin and piperacillin-tazobactam, and 12.9% included Fluoroquinolones (mostly levofloxacin). Regarding clinical outcome indexes, the rate of re-hospitalization was comparable (P = 0.325) between patients with (37.5%) and without polymyxin E (Colistin) (15.38%) as a part of their definite antibiotic therapy regimen. The mortality rate was also comparable (P = 1) between patients with (22.22%) and without colistin (16.67%). In contrast, the median lengths of both hospital and ICU stay were significantly lower (P = 0.015) in patients who did receive colistin (22 days) than those not given colistin as a part of their definite antibiotic therapy regimen (32 days).

Table 4
Frequency and meantime usage of a different class of antibiotics in post pediatric liver transplantation in an empirical or therapeutic setting (N = 80)

Antibiotic class	Frequency of use	Usage period (mean ± SD) or (median [IQR: 25–75])
Carbapenems	35	12 [7–19]
Vancomycin	34	14.29 ± 9.08
Metronidazole	28	7 [5–12]
Beta lactam- beta Lactamase inhibitors	15	12.73 ± 7.00
Fluoroquinolone	15	10.86 ± 8.30
Colistin	9	15 [12.5–56]
Aminoglycoside	8	6.75 ± 4.52
Linezolid	7	22.71 ± 14.08
Cephalosporines	3	2[1–5]
Clindamycin	3	4[2–7]
Macrolides	2	5.5 ± 2.12
Sulfonamide	2	13[11–21]
Notes		
Abbreviations: SD: Standard deviation; IQR: Interquartile range		

Although the median duration of mechanical ventilation was lower in patients under meropenem + vancomycin empiric antibiotic therapy than those given piperacillin-tazobactam + vancomycin (2 and 8 days, respectively), this difference did not reach the statistical significance (P = 0.119). Similarly, the mean (95% confidence interval) changes of CRP level (22.289 mg/dl, -62.273 to 17.696 mg/dl), Whole blood cell (WBC) (2.332 cells/µl, -6.585 to 1.921 cells/µl) and body temperature (0.132 centigrade, -0.237 to 0.501 centigrade) during the course of empiric therapy were comparable between patients under meropenem + vancomycin and those who received piperacillin-tazobactam + vancomycin (P = 0.235, P = 0.268, and P = 0.463).

3. Discussion

In pediatric LT, postoperative bacterial infections occur frequently and are potentially life-threatening. In this one-year, retrospective study, an incidence of 67.9% infection rate was observed, which was higher than a previous study in Iran, reporting an incidence of 54.3% bacterial infection among liver transplant pediatrics. [17]. Our findings are also in accordance with the limited reports worldwide regarding LT in pediatrics (51.9% in Germany and 70.8% in France). [18–22]. In a 23-year, retrospective single-center

study conducted by Kukreti et al, 49 incidents of microbiologically documented infection were observed among 145 pediatrics (34%) in post LT, which 79% had bacterial infections only during their stay in the pediatric ICU. [23]. Numerous factors have contributed to the amplified risk of by bacterial etiology in post-LT pediatrics especially during the early periods; including the difficulty of surgical procedures; high levels of immune suppression because of rejection; numerous points of access for microorganisms (eg probes, catheters, incisions); and patient's poor health state [10, 18, 19, 23, 24].

Based on our results, more than 64.06% of the isolated pathogens were Gram-negative and 35.93% were gram-positive. Our data regarding the proportion of causative pathogens is in accordance with the previous study among post-liver transplant pediatrics in Iran, which showed Gram-negative isolates were comparatively as common as Gram-positive isolates (51% vs 49%), with a predominance of Enterococcus *spp* (36.1%) and *Staphylococcus spp* (11.1%) as Gram-positive bacteria and *Enterobacteriaceae* (21.3%), *Acinetobacter spp* (16.7%), as Gram-negative ones. Gram negative predominance may be due to various factors such as LT patients' longer stay in the ICU, longer duration of mechanical ventilation, along with the possibility of kidney failure after transplantation and the need for dialysis, as well as a long history of the use of preoperative broad-spectrum antibiotics due to recurrent hospitalizations and also biliary tract manipulation during surgery, all of which are risk factors for gram-negative infections [25, 26].

However, some studies have demonstrated a predominance of Gram-positive bacteria; such as in a French study, bacterial isolates showed a dominance of Gram-positive bacteria (78%) which included *Staphylococcus aureus* (32%) and *Staphylococcus epidermis* (26%). It is also worth mentioning that all patients in that study were administered gentamicin, polymyxin, and nystatin during the time of their ICU stay for selective intestinal decontamination or until resumption of oral intake in order to reduce not only the predominance of Gram-positive bacteria, but also the Gram-negative aerobic bacteria in the intestinal flora [19, 27, 28].

Another concern for pathogens causing infection after transplantation is the emergence of resistant species such as MDR, XDR, and VRE. The results of our studies showed that about 25% of gram-negative species isolated from patients were XDR type; other studies in this field also pointed to the high incidence of MDR and XDR pathogens after solid organ transplantation [29–31].The increase in rates of resistant pathogen species not only affects the efficiency of common antibiotic regimes, but also increases the mortality rate [32, 33].Inappropriate administration of antibiotics in empirical conditions, longer hospital and ICU stays, frequent prescription of broad-spectrum antibiotics such as carbapenems and fluoroquinolones in treatment of spontaneous bacterial peritonitis conditions before LT, as well as the need for hemodialysis or Continuous Renal Replacement Therapies (CRRT) after LT are among the risk factors for emerging resistant pathogens after LT [25, 32].

In the case of gram-positive pathogens, the incidence of VRE infections has been reported to be about 31% in our study, while in the study of Pouladfar et al., 82% of Enterococcus species were VRE [17]. The reasons for this difference in the incidence of VRE can be attributed to the establishment and

implementation of stewardship antibiotic programs in our hospital under the supervision of infectious disease and clinical pharmacist specialists in recent years, which has led to a dramatic reduction in the use of inappropriate broad-spectrum antibiotics such as vancomycin.

Our study revealed that Intra-abdominal Surgical Site Infections (SSI) were the most common site of infections in post-liver transplant patients. Based on the studies exploring infection in hospitalized pediatrics during the early periods after LT, the two most frequent sites of infection. [19, 22, 23] were the blood and abdomen. Execution of complex surgical procedures in LT pediatrics and the requirement for insertion of intra-abdominal JP Drain and central vein catheter can have a major impact on the developing infections in the abdomen and blood.

Based on our results, length of stay in ICU and hospital, length of mechanical ventilation after transplant, re-hospitalization and mortality rate were significantly higher in the infected group rather than in non-infected pediatrics. Furthermore, multivariate regression analysis showed that the only risk factor for bacterial infections after LT in pediatrics is the length of stay in the ICU. Factors such as a longer hospitalization and longer stay in ICU have been formerly described to be linked with increased infection in LT by other authors [17, 34, 35]. Although our study revealed that the tacrolimus level was higher in the infected group compared to the non-infected group, no statistical significance was observed. Dohna Schwake et al. demonstrated tacrolimus levels above 20 ng/ml were associated with a higher risk for bacterial infection, especially severe sepsis, septic shock, and SSI. However, this may be due to the complete avoidance of steroids in the absence of rejection in their study in which as a consequence, tacrolimus trough level targets might have been higher [36].

One of the goals of this study was to evaluate the success rate of different antibiotic regimens in empirical as well as definitive therapy. The results of our study showed that receiving carbapenem along with vancomycin, as an empirical regimen, shortens the mechanical ventilation duration compared to beta lactam -beta lactamase inhibitors, although non-significant. Nevertheless, neither of the two regimens was superior in reducing the signs and symptoms of infection. Although the use of carbapenems in the empirical treatment may seem to be necessary with the increase of MDR pathogen species amongst LT, the results of our study showed no difference regarding the administration of carbapenems compared to beta lactam- beta lactamase inhibitors, which is also supported by other studies [37–39].

Given that the use of carbapenems increases the risk of carbapenem-resistant Enterobacteriaceae pathogens [40], some studies have compared the efficacy of carbapenems with beta lactam- beta lactamase inhibitors, especially in the management of ESBL species. This suggests that the use of piperacillin-tazobactam might be a promising alternative to carbapenems for the management of Enterobacteriaceae bloodstream infections, especially when MIC piperacillin-tazobactam is low (MIC ≤ 0.5/4 µgL) or the source of bloodstream infection is the genitourinary tract or abdomen [37]. Furthermore, some studies have also suggested that piperacillin-tazobactam may be a potential alternative to carbapenems in the treatment of AmpC-producing Enterobacteriaceae [41].However, further studies are

essential to provide a more accurate and definitive assessment of the effectiveness against beta lactam - beta lactamase inhibitors versus carbapenems, especially since some studies still consider carbapenems to be superior to others regimes [37, 41]. Furthermore, no studies have been conducted in this regard on pediatric LT until now.

Given the increasing trend of gram-negative XDR species, especially in the case of *Acinetobacter* pathogen, the use of polymyxin E (colistin) is inevitable. In our study, it was found that pediatrics receiving colistin had a significantly shorter length of stay in the ICU and hospital than those who did not receive colistin; however, no significant difference was observed in other factors such as mortality. Given that the number of patients receiving colistin in our study was low (n = 9), the generalization of their results is impossible. However, the results of other studies showed that in the treatment of XDR Acinetobacter baumannii (XDR- Ab) colistin-free regimen is not very successful, and a combination of colistin with carbapenems is most successful in the treatment of these pathogens [30].

The results of our study should be carefully evaluated because it suffers from some limitations; only bacterial infections were evaluated and other infections such as fungal and viral ones were not investigated. Also, the study is the result of a one-year evaluation, so more accurate results may be obtained by evaluating the patients during a longer period. Furthermore, lack of detailed information about the isolated pathogens, including the study of resistance genotypic patterns and the MIC value for MDR and XDR species, and also unavailability of some antibiotics in our centers, such as tigecycline or ceftazidime- avibactam, were the other limitations of our study.

4. Conclusion

Pediatric patients in the immediate postoperative period after LT have a high risk of bacterial infections, which induce morbidity and mortality. To sum it up, a high incidence of bacterial infection was observed among hospitalized pediatrics in the early period after LT. These infections were associated with longer hospital stays and higher mortality rates. Aside from longer ICU stay, there was no other risk factor associated with contracting an infection in multivariate analysis. Furthermore, the use of Piperacillin-tazobactam instead of carbapenems in empirical treatment may be rational.

Declarations

Ethics approval and consent to participate:

The present study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences. The purpose of this study was completely explained to the patient and their parents and were assured that their information will be kept confidential by the researchers. The written consent form was obtained from the patient's parents

Consent for publication

Consent was obtained from the parents of the patient regarding the publication of this case report.

Availability of data and material

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MS and AV desgined the study. NP collected the data and KK carried out the statistical analysis. RS drafted the manuscript. MS and AV revised and proofread the manuscript. All authors read and approved the final version of the manuscript.

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