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ORIGINAL RESEARCH

Drug Resistance and Risk Factors for Acquisition of Gram-Negative Bacteria and Carbapenem-Resistant Organisms Among Liver Transplant Recipients

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ABSTRACT

Introduction: Infections caused by Gram-negative bacteria, in particular carbapenem-resistant organisms (CRO), pose a great threat to liver transplant (LT) recipients. Understanding the risk factors for Gram-negative and CRO infections and the drug resistance of corresponding bacteria will help guide the prevention and treatment of these infections.

Methods: Data on the composition, distribution and drug resistance of Gram-negative bacteria and CRO among LT recipients were collected. The risk factors for Gram-negative and CRO infections were identified via univariate and multivariate analysis.

Results: A total of 45 episodes of Gram-negative infection, including 20 episodes of CRO infection, occurred in 19.9% (27/136) of LT recipients. *Klebsiella pneumoniae* was the dominant pathogenic bacteria (14/45; 31.1%). The most common site of infection was the abdominal cavity/bile duct (11/27; 40.7%). Eleven (8.1%) patients died within 2 months after LT, and two deaths were related to Gram-negative infection. Gram-negative bacteria were relatively sensitive to tigecycline and polymyxin B, with resistance of 26.7 and 11.1%, respectively. CRO had lower resistance to ceftazidime/avibactam (45.5%) and polymyxin B (10%). A univariate analysis showed that male sex, infection within 2 months prior to LT, duration of surgery $\geq$ 400 min, reoperation, indwelling urethral catheter use $\geq$ 3 days and elevated alanine aminotransferase on day 1 post-LT were associated with Gram-negative infection. Multivariate logistic regression analysis revealed that infection within 2 months prior to LT [odds ratio (OR) = 4.426, 95%CI: 1.634–11.99, P = 0.003], duration of surgery $\geq$ 400 min

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[OR = 3.047, 95%CI: 1.194–7.773, $P = 0.02$] and indwelling urethral catheter use ≥ 3 days [OR = 5.728, 95%CI: 1.226–26.763, $P = 0.026$] were independent risk factors for Gram-negative infection after LT, and that only carbapenem use ≥ 3 days within 15 days prior to infection [OR = 14, 95%CI: 1.862–105.268, $P = 0.01$] was related to the occurrence of CRO infections.

Conclusion: The incidence of Gram-negative and CRO infections was high in the early post-LT period. The most common infection site was the abdominal cavity/bile duct, and the dominant pathogen was *K. pneumoniae*. Patients with infections within 2 months prior to LT, prolonged surgery time or delayed urethral catheter removal were prone to Gram-negative infection. Carbapenem exposure was correlated with CRO infections.

Keywords: Liver transplantation; Gram-negative infection; Carbapenem-resistant organism; Risk factors; Drug resistance

Key Summary Points

Why carry out this study?

Gram-negative infections, in particular from carbapenem-resistant organisms (CRO), pose a great threat to liver transplant (LT) recipients. Although the risk factors for various types of infection have been investigated among LT recipients, Gram-negative bacteria and CRO as a whole have rarely been studied to confirm these risk factors.

This study aimed to investigate the prognosis, composition, distribution, drug resistance and risk factors for Gram-negative and CRO infections within 2 months after LT, in order to explore prevention and control strategies for these infections.

What was learned from the study?

The incidence of Gram-negative and CRO infection was high in the early post-LT period. The most common site was the abdominal cavity/bile duct, and the dominant pathogen was *K. pneumoniae*. Gram-negative bacteria were relatively sensitive to tigecycline and polymyxin B. CRO had a relatively lower prevalence of resistance to ceftazidime/avibactam and polymyxin B. Patients with infection within 2 months prior to LT, prolonged surgery time or delayed urethral catheter removal were prone to Gram-negative infections, and carbapenem exposure was correlated with CRO infection.

The results of this study revealed that ceftazidime/avibactam and polymyxin B may be optimal antimicrobial drugs for CRE and CRO, respectively. Strategies for reducing post-LT Gram-negative and CRO infections must include avoiding LT for candidates with infection, avoiding the use of carbapenem antibiotics, and shortening urethral catheter use time and duration of surgery.

INTRODUCTION

Advances in organ acquisition, surgical techniques, early management of postoperative complications and immunosuppressive drugs have made liver transplantation (LT) an optimal therapeutic option for end-stage liver disease [1]. However, LT recipients are prone to developing bacterial infections, with incidence ranging from 33 to 68%, owing to multiple organ dysfunction, impaired immune function, frequent preoperative infection, prolonged operation time, severe surgical trauma and extensive use of broad-spectrum antibiotics after LT [2–6].

At present, the incidence of Gram-negative infections following LT is on the rise [7]. Gram-negative infections account for 31.6–53% of all infections after LT, and carbapenem-resistant

organisms (CRO) in particular pose a great threat to LT recipients [8, 9].

Although the risk factors for various types of infection have been investigated among LT recipients, Gram-negative bacteria and CRO as a whole have rarely been studied [10]. Identifying these infections in high-risk patients will help prevent their emergence and improve the long-term prognosis for LT recipients. Therefore, this study analyzed the composition, distribution, drug resistance, prognosis and risk factors for Gram-negative and CRO infections occurring within 2 months after LT, as well as strategies for the prevention and control of these infections.

METHODS

Study Population and Data Collection

This pathogen-based and retrospective study comprised LT recipients with or without Gram-negative infection. The clinical, laboratory and microbiological laboratory data of 136 LT recipients of grafts from donation after citizens' death were collected in the Third Xiangya Hospital of Central South University from 1 January 2020 to 31 October 2021. The study included 112 male and 24 female patients aged 19 to 68 years. Recipients' underlying diseases included liver cirrhosis/necrosis or tumor due to hepatitis B (102 cases), hepatitis C or E cirrhosis (6 cases), mixed cirrhosis (8 cases), alcoholic cirrhosis (7 cases), autoimmune hepatitis (4 cases), liver failure after LT (3 cases), Budd-Chiari syndrome (2 cases), hepatolenticular degeneration (2 cases), cryptogenic cirrhosis (1 case) and drug-induced liver failure (1 case). All surviving LT recipients were followed up for 2 months. Relevant data were obtained by reviewing electronic medical records.

Inclusion and Exclusion Criteria

We included all adult LT recipients in our hospital during the study period. Recipients who were younger than 18 years of age, experienced active infection within 2 weeks before LT or died of other causes during the perioperative period, such as anesthesia accidents or surgical complications, were excluded. A total of 137 LTs were performed during the study period, and one recipient who died of intraoperative hemorrhage was excluded from the study.

Definition

Pre-LT antibiotic use was defined as receiving broad-spectrum antibiotics for at least 5 days before LT [11]. Reoperation referred to retransplantation or post-LT laparotomy. Carbapenem non-susceptibility referred to strains of minimal inhibitory concentration (MIC) > 2 mg/L [12]. CRO included carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), *Acinetobacter baumannii* (CRAB) and Enterobacteriaceae (CRE) [13]. The strain was considered to be non-susceptible to polymyxin B when the MIC of polymyxin B was > 2 μg/mL [14]. Bacteremia and other infections were determined according to Centers for Disease Control and Prevention National Healthcare Safety Network (CDC NHSN) standards [15]. The source of infection was defined as a culture-positive site of infection accompanied by clinical signs of active infection. Infection-related death was defined as mortality associated with positive culture along with clinical evidence of active infection [15].

Therapeutic Method

All patients underwent modified piggyback LT with tracheal intubation under general anesthesia. Cholecystectomy of the donor liver was performed routinely, and a T-tube was placed for biliary drainage in a few patients. Each recipient received prophylactic administration of third-generation cephalosporin or carbapenem antibiotics, teicoplanin, daptomycin or linezolid as needed to prevent bacterial infection. Caspofungin was used if necessary to prevent fungal infection. The antibiotic treatment was generally maintained for 5–7 days. Intestinal decontamination was not performed. Polymyxin or ceftazidime/avibactam was administered to patients with suspected or confirmed severe infection caused by CRO,

since these pathogens result in life-threatening infections.

Most of the recipients were given basiliximab 20 mg together with methylprednisolone 500 mg intravenously for immune induction. Some patients received basiliximab 20 mg on the fourth postoperative day. Tacrolimus (0.1 mg/kg/day in two doses) or ciclosporin A (6–7 mg/kg/day in two doses) and corticosteroids (initiated at a dose of 300–500 mg and then tapered over 7 days to 5–20 mg/day) were used initially for immunosuppressive maintenance therapy. Mycophenolate mofetil or mycophen and anti-thymocyte globulin were given as required.

Microbial Culture Method

Blood was collected intravenously from two sites at the same time under aseptic procedures for culture. After collecting 8–10 mL of blood, a 25 mL aerobic/anaerobic culture flask was used to store the blood. Blood and other samples, including sputum, abdominal drainage fluid, bile, urine, cerebrospinal fluid and bronchoalveolar lavage fluid, were immediately sent to the microbiology laboratory for bacterial culture. Blood samples were cultured and monitored by a BD BACTEC 9240 automatic blood culture instrument (Becton Dickinson, USA). Species were identified using the VITEK 2 system (bioMerieux, Marcy l'Etoile, France). Antimicrobial susceptibility and MIC were determined by the broth microdilution method. The intermediate susceptibility was considered to be resistant.

Ethics

The Institutional Review Board of the Third Xiangya Hospital of Central South University endorsed this study protocol prior to data collection (number: 22036). The Institutional Review Board approved the waiver of patient informed consent because this was a retrospective cohort study whose information was obtained from electrical medical records, and the study involved no direct intervention with the enrolled patients; in addition, the data were de-identified and anonymously analyzed. Our study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Statistics

The SPSS 26.0 statistical software package (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for statistical analysis of data. Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), and classified data were expressed as a percentage. Pearson's chi-square test or Fisher's exact test was used for univariate comparisons of differences between two groups. Variables with $P < 0.05$ in univariate analysis were introduced into the final multivariate model. Multivariate logistic regression was applied for multivariate analysis based on forward stepwise logistic regression. Odds ratio (OR) values and 95% confidence intervals (95%CI) were used to describe the independent factors associated with Gram-negative and CRO infections. When $P < 0.05$ in the two-tailed test, the difference was considered to be statistically significant.

RESULTS

General Characteristics and Prognosis of LT Recipients

A total of 137 recipients underwent LT in the Third Xiangya Hospital of Central South University from 1 January 2020 to 31 October 2021, of whom 136 were included in this retrospective study. Demographic, laboratory and clinical data from the 136 LT recipients are shown in Table 1. The average age of patients was 45.8 (range 19–69) years, and 112 (82.4%) were male. The median (IQR) length of hospital stay prior to LT was 11.5 (1–30) days. The median (IQR) preoperative Model for End-Stage Liver Disease (MELD) score was 23.5 (15–29). Seventy-one patients (52%) received antibiotics within 2 weeks prior to LT. Sixty-five patients

Table 1 Demographic, laboratory and clinical variables of 136 liver transplant recipients

Characteristics	Value
Age, mean years ± SD	45.8 ± 10.2
Recipient gender, no. of male (%)	112 (82.4)
Underlying liver diseases, *n* (%)	
Viral cirrhosis/necrosis/tumor	
Hepatitis B	102 (75)
Hepatitis C or E	6 (4.4)
Alcoholic cirrhosis	7 (5.1)
Autoimmune hepatitis	4 (2.9)
Mixed cirrhosis	8 (5.9)
Others	9 (6.6)
Pre-LT diabetes, *n* (%)	20 (14.7)
Pre-LT creatinine, median (IQR), mg/dL	0.8 (0.7–1)
Infection within 2 months prior to LT, no. of cases (%)	65 (47.8)
Pre-LT antibiotic use, *n* (%)	71 (52.2)
Hospital stay prior to LT, median (IQR), days	11.5 (1–30)
MELD score at LT, median (IQR)	23.5 (15–29)
Cold ischemia time, median (IQR), h	5.7 (4.2–7.3)
Intraoperative bleeding, median (IQR), mL	3000 (2000–4425)
Intraoperative RBC transfusion, median (IQR), units	12.5 (9–17.4)
Duration of surgery, median (IQR), min	370 (327–430)
Patient immunosuppressant treatment post-LT, no. of cases (%)	
Tacrolimus	135 (99.3)
Ciclosporin A	1 (0.7)
Mycophenolate mofetil	79 (58.1)
Enteric-coated mycophenolate sodium	13 (9.6)
Glucocorticoid	136 (100)
Anti-thymocyte globulin, *n* (%)	8 (5.9)
Basiliximab, *n* (%)	121 (89)
Exposure to more than two intravenous antibiotics post-LT, *n* (%)	36 (26.5)
Mechanical ventilation post-LT, *n* (%)	8 (5.9)
Reoperation, *n* (%)	7 (5.1)
SOFA score on day 7 post-LT, median (IQR)	3.5 (2–5)
Duration of indwelling urethral catheter, median (IQR), days	3 (2–4)
Duration of intraperitoneal catheterization, median (IQR), days	16 (14–19.8)
Acute rejection, *n* (%)	15 (11)
Time of 45 infectious episodes, no. of episodes (%)	
≤ 7 days post-LT	30 (66.7)
8–30 days post-LT	13 (28.9)
31–60 days post-LT	2 (4.4)
Types of infection, no. of cases (%)	
Abdominal cavity/bile duct infection	7 (5.1)
Pneumonia	6 (4.4)
Urinary tract infection	4 (2.9)
Bacteremia	2 (1.5)
Multiple-site infection	8 (5.9)
Laboratory variables from blood	
WBC count prior to LT < 4000/mm^3, *n* (%)	44 (32.4)
Lymphocyte count prior to LT < 500/mm^3, *n* (%)	41 (30)
Platelet count prior to LT < 50,000/mm^3, *n* (%)	42 (30.9)
Albumin level prior to LT, median (IQR), g/L	33.4 (30.6–36.6)
ALT on day 1 after LT, median (IQR) U/L	702 (426–1312.8)

Table 1 continued

Characteristics	Value
Creatinine on day 3 after LT, median (IQR), mg/dL	0.8 (0.7–1.3)
All-cause mortality, *n* (%)	11 (8.1)
Gram-negative infection-related mortality, *n* (%)	2 (1.5)

ALT, alanine aminotransferase; IQR, interquartile range; LT, liver transplant; MELD, Model for End-Stage Liver Disease; RBC, red blood cell; SD, standard deviation; SOFA, sequential organ failure assessment; WBC, white blood cell

(47.8%) were infected within 2 months but not within 2 weeks before LT.

The dominant primary liver diseases were liver cirrhosis/necrosis or tumor due to hepatitis B, mixed liver cirrhosis and alcoholic cirrhosis, with 102 (75%), eight (5.9%) and seven (5.1%) cases, respectively. Six of eight patients with mixed liver cirrhosis had disease complicated by hepatitis B. Twenty patients (14.7%) had type 2 diabetes before LT. In total, 121 and eight recipients received immune induction therapy with basiliximab and anti-thymocyte globulin, respectively. A total of 135 (99.3%) and 79 (58.1%) recipients received tacrolimus and mycophenolate mofetil as immune maintenance therapy, respectively.

The median (IQR) sequential organ failure assessment (SOFA) score on day 7 post-LT was 3.5 (2–5). Eleven patients died within 2 months after LT, five of whom developed CRO infection. One patient each died of intracranial hemorrhage of unknown cause, hemorrhagic shock caused by ulcerative bleeding of the esophagus, liver failure attributable to severe rejection and asphyxia due to acquired myasthenia gravis. One patient each died as a result of pneumonia caused by *Pneumocystis jirovecii*, severe pneumonia and multiple organ dysfunction by *Aspergillus fumigatus* and *A. baumannii*, intra-abdominal infection by *A. baumannii*, bloodstream infection ascribed to *Enterococcus faecium* combined with *Candida krusei*, pneumonia along with urinary tract infection due to *E. faecium* and bacteremia due to *E. faecium*. Another patient died of brain abscess with cerebral hernia with a negative cerebrospinal fluid culture on the 30th day after LT. Among these 11 recipients who died, six were cases of Gram-negative infection after LT and two were Gram-negative infection-related. The median (IQR) SOFA score on day 7 post-LT was 5 (3–5) in these 11 patients who died, higher than the remaining 125 surviving patients, whose median (IQR) SOFA score on day 7 post-LT was 3 (2–5). Univariate analysis showed that a SOFA score of 5 or more ($P = 0.048$) and Gram-negative infection ($P = 0.003$) were associated with greater risk of death.

Classification of Causative Pathogens and the Site and Timing of Infection

A total of 45 strains of Gram-negative bacteria were isolated from 27 (19.9%) of 136 LT recipients, including 20 CRO isolated from 15 (11.0%) recipients. The most frequent pathogens were *Klebsiella pneumoniae* (14/45; 31.1%), *A. baumannii* (11/45; 24.4%) and *Stenotrophomonas maltophilia* (5/45; 11.1%). The other Enterobacteriaceae included three isolates of *Escherichia coli* and one isolate each of *Enterobacter cloacae*, *Enterobacter aerogenes* and *Salmonella enteritidis*. The other non-fermentative bacteria included two isolates of *P. aeruginosa*, and one isolate each of *Acinetobacter pittii*, *Acinetobacter johnsonii*, *Burkholderia cepacia*, *Sphingomonas paucimobilis*, *Shewanella putrefaciens* and *Ralstonia pickettii*. Table 1 shows that the most common types of infection were multiple-site infection (8/27; 29.7%), abdominal cavity/bile duct infection (7/27; 25.9%) and pneumonia (6/27; 22.2%). There were eight patients with multiple-site infections and eight with multiple Gram-negative bacteria. Among the eight patients with multiple-site infections, six had bacteremia, four had abdominal cavity infection, four had pneumonia and three had urinary tract infection. Among eight patients with multiple Gram-negative bacteria, four were co-infected with Gram-positive bacteria and/or

fungi including two with *Enterococcus faecium*, and one each with *Staphylococcus aureus* and *Enterococcus faecium* plus *Candida krusei*. Forty-three (95.6%) of the 45 episodes of infection occurred within 1 month and 30 (66.7%) within 1 week after LT.

Drug Resistance of Gram-Negative Bacteria and CRO

Table 2 shows that the prevalence of resistance of Gram-negative bacteria to cefuroxime (75.6%), piperacillin/tazobactam (73.3%), aztreonam (68.9%), imipenem/cilastatin (62.2%) and meropenem (60%) was 60% or above. Gram-negative bacteria isolated were relatively sensitive to cefoperazone/sulbactam, tigecycline and polymyxin B, with resistance prevalence of 48.9%, 26.7% and 11.1%, respectively. Table 3 revealed that there were 20 CRO out of these 45 Gram-negative bacteria, including nine CRE, nine CRAB and two CRPA. CRO had a relatively lower prevalence of resistance to ceftazidime/avibactam (45.5%), tigecycline (55.5%) and polymyxin B (10%). CRE had a high rate of sensitivity to ceftazidime/avibactam (89.9%). Of all CRO, only a *R. pickettii* strain was resistant to polymyxin B.

Treatment Choices and Results of the Treatment in 15 Patients with CRO Infections

Five patients with *A. baumannii* infection were cured by polymyxin B alone or in combination with meropenem. One patient each with infection from *K. pneumoniae* and from *A. baumannii* with *K. pneumoniae* co-infection was cured by polymyxin B in combination with ceftazidime/avibactam. One patient with pneumonia due to *K. pneumoniae* was cured by ceftazidime/avibactam. One patient with *K. pneumoniae* infection was cured by ceftazidime/avibactam plus meropenem. Meropenem alone was

Table 2 Antimicrobial resistance of 45 Gram-negative bacteria to 13 commonly used antibiotics

Antimicrobial	*K. pneumoniae* (*n* = 14)	Other Enterobacteriaceae (*n* = 6)	*A. baumannii* (*n* = 11)	*S. maltophilia* (*n* = 5)	Other non-fermentative bacteria (*n* = 8)	Total strains (*n* = 45)
Amikacin	5 (35.7)	1 (16.7)	9 (81.8)	5 (100)	3 (37.5)	51.1
Levofloxacin	9 (64.3)	4 (66.7)	10 (90.9)	0 (0)	2 (25)	55.6
Cefuroxime	6 (42.9)	6 (100)	11 (100)	5 (100)	6 (75)	75.6
Ceftazidime	6 (42.9)	4 (66.7)	9 (81.8)	0 (0)	4 (50)	51.1
Cefepime	7 (50)	2 (33.3)	10 (90.9)	0 (0)	6 (75)	55.6
Aztreonam	6 (42.9)	4 (66.7)	10 (90.9)	5 (100)	6 (75)	68.9
Piperacillin/tazobactam	9 (64.3)	3 (50)	10 (90.9)	5 (100)	6 (75)	73.3
Cefoperazone/sulbactam	6 (42.9)	3 (50)	9 (81.8)	0 (0)	4 (50)	48.9
Meropenem	6 (42.9)	1 (16.7)	9 (81.8)	5 (100)	6 (75)	60.0
Imipenem/cilastatin	6 (42.9)	2 (33.3)	9 (81.8)	5 (100)	6 (75)	62.2
Tigecycline	5 (35.7)	1 (16.7)	4 (36.4)	0 (0)	2 (25)	26.7
Polymyxin B	1 (7.1)	0 (0)	0 (0)	0 (0)	4 (50)	11.1
Sulfamethoxazole	7 (50)	3 (50)	9 (81.8)	0 (0)	6 (75)	55.6

Table 3 Antimicrobial resistance of 20 CRO to 15 commonly used antibiotics

Antimicrobial	*K. pneumoniae* (*n* = 6)	Other Enterobacteriaceae (*n* = 3)	*A. baumannii* (*n* = 9)	*P. aeruginosa* (*n* = 2)	Total strains (*n* = 20)
Amikacin	5 (83.3)	0 (0)	9 (100)	0 (0)	70
Levofloxacin	6 (100)	2 (66.7)	9 (100)	1 (50)	90
Cefuroxime	6(100)	3(100)	9(100)	2(100)	100
Ceftazidime	6(100)	1(33.3)	9 (100)	2 (100)	90
Cefepime	6 (100)	0 (0)	9 (100)	2 (100)	85.5
Aztreonam	6 (100)	2 (66.7)	9 (100)	2 (100)	95.5
Piperacillin/tazobactam	6 (100)	3 (100)	9 (100)	2 (100)	100
Cefoperazone/sulbactam	6 (100)	3 (100)	9 (100)	2 (100)	100
Ceftazidime/avibactam	0 (0)	1 (33.3)	8 (88.9)	0 (0)	45.5
Meropenem	6 (100)	1 (33.3)	9 (100)	2 (100)	90
Imipenem/cilastatin	6 (100)	2 (66.7)	9 (100)	2 (100)	95.5
Ertapenem	6 (100)	3 (100)	9 (100)	2 (100)	100
Tigecycline	4 (66.7)	1 (33.3)	4 (44.4)	2 (100)	55.5
Polymyxin B	1 (16.7)	1 (33.3)	0 (0)	0 (0)	10
Sulfamethoxazole	6 (100)	2 (66.7)	9 (100)	2 (100)	95.5

prescribed to three patients with infection from *E. coli*, *E. cloacae* or *E. aerogenes* and eradicated these strains. One patient with *P. aeruginosa* pneumonia was successfully treated with polymyxin B. Two patients, one infected with *A. baumannii* and one with *A. baumannii* along with *P. aeruginosa*, were treated unsuccessfully with tigecycline alone and polymyxin B plus imipenem/cilastatin, respectively.

Analysis of Risk Factors for Gram-Negative and CRO Infections

Table 4 reveals that in univariate analysis, male sex ($P = 0.017$), infection within 2 months prior to LT ($P = 0.002$), duration of surgery $\geq$ 400 min ($P = 0.024$), reoperation ($P = 0.04$), indwelling urethral catheter use $\geq$ 3 days ($P = 0.01$) and elevated alanine aminotransferase on day 1 post-LT ($P = 0.039$) were associated with Gram-negative infection. These six variables significant in the univariate analysis were included in a multivariate logistic regression analysis, which identified that infection within 2 months prior to LT [OR = 4.426, 95%CI: 1.634–11.99, $P = 0.003$], duration of surgery $\geq$ 400 min [OR = 3.047, 95%CI: 1.194–7.773, $P = 0.02$] and indwelling urethral catheter use $\geq$ 3 days [OR = 5.728, 95%CI: 1.226–26.763, $P = 0.026$] were independent risk factors for Gram-negative infection after LT.

As shown in Table 5, univariate analysis revealed that duration of carbapenem use $\geq$ 3 days within 15 days prior to infection ($P = 0.003$) and intraoperative bleeding $\geq$ 3000 mL ($P = 0.021$) were associated with CRO infection. Both statistically significant variables in the univariate analysis were introduced into a multivariate logistic regression analysis. However, the final multivariate model confirmed that only duration of carbapenem

Table 4 Univariate and multivariate logistic regression analysis of risk factors for Gram-negative infection in liver transplant recipients

Characteristics	Control group (n = 109)	Gram-negative infection group (n = 27)	P	OR (95% CI)
Total, n (%)				
Univariate analysis				
Age ≥ 55 years, n (%)	20 (18.3)	9 (33.3)	0.089	
Male sex, n (%)	94 (86.2)	18 (66.7)	0.017	0.536 (0.135–2.120)
Hepatic cirrhosis/necrosis or tumor due to hepatitis B	84 (77.1)	18 (66.7)	0.264	
Alcoholic cirrhosis	4 (3.7)	3 (11.1)	0.28	
Pre-LT diabetes	16 (14.7)	4 (14.8)	0.986	
Pre-LT creatinine > 1.5 mg/dL, n (%)	7 (6.4)	2 (7.4)	1	
Infection within 2 months prior to LT, n (%)	45 (41.3)	20 (74.1)	0.002	5.434 (1.161–25.431)
Pre-LT antibiotic use, n (%)	56 (51.4)	15 (55.6)	0.697	
Hospital stay prior to LT ≥ 7 days, n (%)	68 (62.4)	17 (63)	0.956	
MELD score ≥ 25, n (%)	51 (46.8)	13 (48.1)	0.899	
Cold ischemia time > 6 h, n (%)	50 (45.9)	15 (55.6)	0.367	
Intraoperative bleeding ≥ 3000 mL, n (%)	61 (56.0)	20 (74.1)	0.086	
Intraoperative RBC transfusion ≥ 8 U, n (%)	91 (83.5)	23 (85.6)	0.83	
Duration of surgery ≥ 400 min, n (%)	35 (32.1)	15 (55.6)	0.024	3.306 (1.162–11.358)
Use of anti-thymocyte globulin, n (%)	5 (4.6)	3 (11.1)	0.197	
Use of basiliximab, n (%)	96 (88.1)	25 (92.6)	0.502	
Dosage of methylprednisolone use post-LT > 1500 mg	54 (49.5)	14 (51.9)	0.83	
Exposure to more than two intravenous antibiotics post-LT	27 (24.8)	9 (33.3)	0.367	
Mechanical ventilation post-LT, n (%)	4 (3.7)	4 (14.8)	0.081	
Reoperation, n (%)	3 (2.8)	4 (14.8)	0.04	4.788 (0.496–46.192)
Indwelling urethral catheter use ≥ 3 days, n (%)	74 (67.9)	25 (92.6)	0.01	9.493 (1.491–60.449)
Acute rejection, n (%)	12 (11)	3 (11.1)	0.988	

Table 4 continued

Characteristics	Control group (n = 109)	Gram-negative infection group (n = 27)	P	OR (95% CI)
WBC count prior to LT < 4000/mm^3, n (%)	38 (34.9)	6 (22.2)	0.209	
Lymphocyte count prior to LT < 500/mm^3, n (%)	36 (33)	5 (18.5)	0.141	
Platelet count prior to LT < 50,000/mm^3, n (%)	36 (33)	6 (22.2)	0.277	
Albumin level prior to LT < 35 g/L, n (%)	65 (59.6)	17 (63)	0.752	
ALT on day 1 post-LT > 1000 μmol/L, n (%)	30 (27.5)	13 (48.1)	0.039	2.639 (0.767–9.085)
Creatinine on day 3 post-LT > 1.5 mg/dL, n (%)	21 (19.3)	7 (25.9)	0.444	
Multivariate analysis				
Male sex			0.181	0.453 (0.142–1.446)
Reoperation			0.092	5.026 (0.767–32.958)
ALT on day 1 post-LT > 1000 μmol/L			0.091	2.394 (0.869–6.597)
Infection within 2 months prior to LT			0.003	4.426 (1.634–11.990)
Duration of surgery ≥ 400 min			0.02	3.047 (1.194–7.773)
Indwelling urethral catheter use ≥ 3 days			0.026	5.728 (1.226–26.763)

ALT, alanine aminotransferase; CI, confidence intervals; LT, liver transplant; MELD, Model for End-Stage Liver Disease; OR, odds ratios; RBC, red blood cell; WBC, white blood cell

use ≥ 3 days within 15 days prior to infection [OR = 14, 95%CI: 1.862–105.268, P = 0.01] was an independent risk factor for CRO infection after LT.

DISCUSSION

Infections caused by Gram-negative bacteria, in particular CRO, are becoming increasingly problematic in LT recipients. We retrospectively reviewed 136 LT patients and found a high occurrence of Gram-negative (19.9%) and CRO (11.0%) infections. We also found that 95.6% of all Gram-negative infections occurred within 1 month after LT. Zhong et al. [10] reported that 30.4% of LT recipients were infected with Gram-negative bacteria. Ferrarese et al. reported that Enterobacteriaceae was responsible for 44.3% of hospital-acquired infections within 1 month after LT. In this regard, *E. coli*, *K. pneumoniae* and *Proteus mirabilis* were the most common pathogens responsible for infection [16]. Non-fermentative bacteria, including *A. baumannii*, *P. aeruginosa* and *S. maltophilia*, were also frequent causative strains of infection after LT. Previous studies showed that the incidence of *P. aeruginosa* infection and *A. baumannii* bacteremia in LT recipients ranged from 1.9 to 15.9% and 0.8–15.9%, respectively [17–19].

CRO infections are increasingly widespread worldwide and are associated with high morbidity and mortality among LT recipients. The incidence of infection caused by CRE, particularly CRKP, ranged from 6 to 12.9% in LT recipients [20]. The present study revealed that more than 80% of *A. baumannii* isolates were carbapenem-resistant, similar to a previous study reporting that more than 50% of *A. baumannii* isolates were CRAB [21]. A multicenter study conducted on LT recipients with CRE infections showed a mortality rate of 28% [22]. Studies by Mouloudi et al. and Pereira et al. demonstrated that CRKP infection was

Table 5 Univariate and multivariate logistic regression analysis of risk factors for CRO infection in liver transplant recipients

Characteristics	CSO (n = 9)	CRO (n = 15)	P	OR (95% CI)
Total, n (%)				
Univariate analysis				
Age ≥ 55 years, n (%)	4 (44.4)	4 (26.7)	0.412	
Male sex, n (%)	6 (66.7)	9 (60)	1	
Hepatic cirrhosis/necrosis or tumor due to hepatitis B	6 (66.7)	10 (66.7)	1	
Pre-LT diabetes	1 (11.1)	3 (20)	1	
Infection within 2 months prior to LT, n (%)	5 (55.6)	12 (80)	0.356	
Pre-LT antibiotic use, n (%)	5 (55.6)	8 (53.3)	1	
Hospital stay prior to LT ≥ 7 days, n (%)	7 (77.8)	8 (53.3)	0.389	
MELD score ≥ 25, n (%)	3 (33.3)	8 (53.3)	0.423	
Cold ischemia time > 6 h, n (%)	7 (77.8)	10 (66.7)	0.669	
Intraoperative bleeding ≥ 3000 mL, n (%)	3 (33.3)	13 (86.7)	0.021	7.362 (1.425–127.473)
Intraoperative RBC transfusion ≥ 8U, n (%)	6 (66.7)	14 (93.3)	0.13	
Duration of surgery ≥ 400 min, n (%)	2 (22.2)	10 (66.7)	0.089	
Use of anti-thymocyte globulin, n (%)	1 (11.1)	1 (6.7)	1	
Use of basiliximab, n (%)	8 (88.9)	15 (100)	0.375	
Dosage of methylprednisolone use post-LT > 1500 mg	4 (44.4)	8 (53.3)	1	
Exposure to more than two intravenous antibiotics post-LT	2 (22.2)	7 (46.7)	0.389	
Mechanical ventilation, n (%)	1 (11.1)	4 (26.7)	0.615	
Reoperation, n (%)	0 (0)	4 (26.7)	0.259	
Indwelling urethral catheter use ≥ 3 days, n (%)	9 (100)	14 (93.3)	1	
Carbapenem use ≥ 3 days within 15 days prior to CSO/CRO infection, n (%)	2 (22.2)	13 (86.7)	0.003	8.069 (1.496–131.235)
WBC count prior to LT < 4000/mm^3, n (%)	2 (22.2)	4 (26.7)	1	
Lymphocyte count prior to LT < 500/mm^3, n (%)	2 (22.2)	3 (20)	1	
Platelet count prior to LT < 50,000/mm^3, n (%)	3 (33.3)	3 (20)	0.635	
Albumin level prior to LT < 35 g/L, n (%)	6 (66.6)	9 (60)	1	
ALT on day 1 post-LT > 1000 μmol/L, n (%)	5 (55.6)	8 (53.3)	1	
Creatinine on day 3 post-LT > 1.5 mg/dL, n (%)	3 (33.3)	4 (26.7)	1	
Multivariate analysis				

Table 5 continued

Characteristics	CSO (n = 9)	CRO (n = 15)	P	OR (95% CI)
Intraoperative bleeding ≥ 3000 mL			0.091	7.011 (0.733–67.028)
Carbapenem use ≥ 3 days within 15 days prior to CSO/CRO infections			0.01	14 (1.862–105.268)

ALT, alanine aminotransferase; CI, confidence intervals; CRO, carbapenem-resistant organism; CSO, carbapenem-sensitive organism; LT, liver transplant; MELD, Model for End-Stage Liver Disease; OR, odds ratios; RBC, red blood cell; WBC, white blood cell

associated with a mortality rate of 35–82% [23, 24]. In the present study, 5 of 15 LT recipients with CRO infections died, and all-cause mortality was 33.3%, consistent with the studies mentioned above. Previous exposure to carbapenems was considered to be predictive of CRO infection, through resistance selection or induction, which was also proved by the present study, since carbapenem exposure for ≥ 3 days prior to infection was related to CRO infection [25].

Clinicians are facing a therapeutic dilemma in treating CRO infections. Fortunately, the polymyxins, including colistin and polymyxin B, remain effective against CRO in most locations worldwide [21]. The present study also revealed that all CRO except a *R. pickettii* strain, which was intrinsically resistant to colistin, were not resistant to polymyxin B [26]. However, polymyxin B monotherapy was frequently associated with heteroresistance. Zusman et al. [27] found that polymyxin–carbapenem combination therapy showed synergy rates of 77% for *A. baumannii*, 50% for *P. aeruginosa* and 44% for *K. pneumoniae*. In 2016, an investigator-initiated, open-label, randomized controlled study involving 360 patients conducted in six centers among three countries showed that a combination of colistin with a carbapenem, in comparison with colistin monotherapy, achieved an absolute improvement in clinical success of 15% against CRO [12]. However, in 2018, when the number of patients was increased to 406, mainly infected with *A. baumannii*, the same researchers found that combination therapy was not superior to monotherapy, and the addition of meropenem to colistin did not improve clinical failure [28]. Furthermore, carbapenem use may favor *Clostridium difficile* infection.

We found that CRO had a higher prevalence of resistance of greater than 90% to carbapenem and lower prevalence of resistance to ceftazidime/avibactam (45.5%) and polymyxin B (10.0%). Therefore, ceftazidime/avibactam and polymyxin B may be optimal antimicrobial drugs for CRE and CRO, respectively. Caston et al. [29] showed that the sensitivity of Enterobacterales to ceftazidime/avibactam was 99.9%, in accordance with our present finding of sensitivity of CRE to ceftazidime/avibactam of 88.9%. CRE-infected patients treated with ceftazidime/avibactam achieved an overall success rate of approximately 70% [30, 31]. According to the present findings, the combination of tigecycline and polymyxin B may be an excellent therapeutic option against CRAB.

Gram-negative bacteria and CRO as a whole have rarely been studied to investigate the risk factors for infections that they cause among LT recipients. Zhong et al. [10] analyzed risk factors for Gram-negative infections among LT recipients and confirmed several independent risk factors, including female sex, higher MELD score, having received pre- and post-LT broad-spectrum antibiotics, prolonged endotracheal intubation (≥ 72 h), presence of biliary complication and lack of prednisone use after LT. Risk factors for post-LT *A. baumannii* infections were also confirmed in several previous studies,

including diabetes, hospital or intensive care unit length of stay, pre-LT MELD score, hemodialysis after LT, reoperation, graft dysfunction, exposure to broad-spectrum antibiotics, particularly previous carbapenems use, septic shock and older recipient age [32–34].

Although donors can pose a risk for Gram-negative infections in recipients, donor-derived transmission of infection remains a rare complication of LT [35]. In the present study, only one recipient experienced donor-derived infection, which was due to CRKP from a donor with pneumonia caused by CRKP. Four other donors had urinary tract infections. However, blood cultures from donors were all negative before the organs were harvested. In view of the above, we did not analyze the association between donors' and recipients' infections.

In univariate analysis, elevated alanine aminotransferase on day 1 post-LT was associated with Gram-negative infection. However, the statistical significance was not maintained in the multivariate analysis. A high post-LT alanine aminotransferase level indicated severe hepatic ischemia–reperfusion injury and similarly severe gastrointestinal ischemia–reperfusion injury that led to impairment of the normal barriers of the gastrointestinal tract and then allowed access of the normal flora to the portal circulation. A high post-LT alanine aminotransferase level also indicated incompetent reticuloendothelial function of the transplanted liver resulting in a reduced ability to remove bacteria from the blood [36]. More research is warranted to establish an association between liver graft function and post-LT infection.

Various studies have tried to identify the risk factors for CRE, CRKP and CRAB infections in LT recipients. CRE-infected patients were more likely to have characteristics of pre-transplant CRE acquisition, pre-LT MELD scores greater than 32, combined liver-kidney transplant, secondary surgery and post-LT renal replacement therapy [37]. Older recipient age, diabetes, chronic kidney disease, colonization with CRKP, a higher MELD score, mechanical ventilation, hemodialysis, exposure to cephalosporin, carbapenem, or piperacillin/tazobactam, hepatitis C virus recurrence and Roux-en-Y biliary choledochojejunostomy were introduced as risk factors for CRKP infections in previous studies [24, 28, 38–40]. On the other hand, fulminant hepatitis as underlying disease, colonization with CRAB before LT, cold ischemia, dialysis following LT, post-LT length of ICU stay, prolonged central venous catheter use and previous exposure to any antibiotic including carbapenem might lead to post-LT CRAB infection [41, 42].

The findings of the present study complement those of previous studies, and indicate that the independent risk factors for Gram-negative infection after LT were infections within 2 months prior to LT, duration of surgery $\geq$ 400 min and indwelling urethral catheter use $\geq$ 3 days, and the predictor of CRO was carbapenem use $\geq$ 3 days within 15 days prior to infection. Our results suggest that these should be cautiously avoided. Antibiotic exposure remained a key risk factor for resistant Gram-negative infections; prior infections meant greater colonization of bacteria, prolonged urethral catheters implied more urinary tract infection and bacterial translocation, and prolonged surgery duration indicated both severe trauma and intestinal bacterial translocation. Therefore, strategies for reducing post-LT Gram-negative and CRO infections must include avoiding performing LT for candidates with infection, avoiding the use of carbapenem antibiotics, and shortening urethral catheter use and duration of surgery.

This study has several limitations, including the relatively small samples and the single-center and retrospective design, which hindered the ability to make a definitive conclusion about the risk factors for Gram-negative and CRO infections. Therefore, future larger prospective studies are needed to confirm our findings. For example, seven and five out of 99 patients with indwelling urethral catheters for $\geq$ 3 days had Gram-negative urinary tract infections and bacteremia, respectively. Surprisingly, seven and six of these 99 patients had Gram-negative abdominal/bile duct infections and pneumonia, respectively, which are seldom caused by delayed urethral catheter removal. This risk factor for post-LT Gram-negative infection requires further study. Furthermore,

we did not routinely monitor CRO colonization among LT candidates. Nevertheless, despite these limitations, we believe this study addresses an important topic, because Gram-negative bacteria, particularly CRO, can lead to potentially life-threatening consequences, and at present, studies on risk factors for Gram-negative and CRO infections as a whole are lacking among LT recipients.

CONCLUSION

The results of this study revealed that the incidence of Gram-negative and CRO infections was high within 2 months after LT and might lead to potentially life-threatening consequences. The most common infection site was the abdominal cavity/bile duct, and the dominant pathogen was *K. pneumoniae*. Patients with infections within 2 months prior to LT, prolonged surgery time or delayed urethral catheter removal were prone to Gram-negative infections. Furthermore, carbapenem exposure was correlated with CRO infections. Based on these results, future larger prospective studies are needed to make a definitive conclusion about the risk factors for Gram-negative and CRO infections.

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Compliance with Ethics Guidelines. The Institutional Review Board of the Third-Xiangya Hospital of Central South University endorsed this study protocol prior to data collection (number:22036). The Institutional Review Board approved the waiver of patient informed consent because this was a retrospective cohort study whose information was obtained from electrical medical records, and this study did not directly interfere with the enrolled patients; in addition, the data were de-identified and anonymously analyzed. Our study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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