

Carbapenems versus Cephalosporin or Piperacillin-Tazobactam as Perioperative Antibiotic Prophylaxis in Liver Transplant Recipients with Model for End-Stage Liver Disease Scores of ≥ 30 : A Retrospective Study in a Chinese Population

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Objective: Perioperative prophylaxis, commonly with a third-generation cephalosporin plus ampicillin or piperacillin-tazobactam, is usually employed to prevent infections in liver transplantation (LT) recipients. Patients with a high Model for End-Stage Liver Disease (MELD) score have an increased infection risk after LT. However, whether carbapenems could be used as surgical prophylaxis in these high-risk patients remains unclear. Therefore, this study aimed at comparing the effectiveness of carbapenems with that of cephalosporin or piperacillin-tazobactam for surgical prophylaxis in high-risk LT recipients with a MELD score ≥ 30 .

Design or Methods: This retrospective study included adult patients with a MELD score ≥ 30 who underwent LT between May 2018 and September 2020. We comparatively analyzed the infection rate and outcome between patients using cefoperazone-sulbactam or piperacillin-tazobactam and those using carbapenems as surgical prophylaxis.

Results: This study included 105 LT recipients. Seventy-eight and 27 patients used non-carbapenem and carbapenem antibiotics, respectively, as surgical prophylaxis. The corresponding infection incidence rates within 30 days were 38.5% and 66.7% ($p = 0.011$). Multivariate analysis revealed that reoperation and the Child–Pugh score were independent risk factors for infections within 30 days after LT. The following four risk factors were associated with the 180-day post-LT survival: MELD score, vascular complication, intra-abdominal bleeding, and infection with carbapenem-resistant organisms (CROs). There was no significant difference in CRO infection incidence between the carbapenem and non-carbapenem groups (18.5% vs 11.5%; $p = 0.345$).

Conclusion: Carbapenem use as surgical prophylaxis was not associated with infection incidence within 30 days after LT, 180-day post-LT survival or CRO infection. Therefore, carbapenems are not superior to cephalosporin or piperacillin-tazobactam for perioperative antibiotic prophylaxis in LT recipients with a MELD score ≥ 30 .

Keywords: perioperative prophylaxis, liver transplantation, infection, carbapenems, carbapenem-resistant organisms

Introduction

Infectious complications are major causes of morbidity and mortality after liver transplantation (LT). Because of the high rate of surgical-site infections (SSIs) in LT patients, perioperative prophylaxis is usually employed.^{1–4} Clinical studies have suggested that perioperative antibiotic prophylaxis is beneficial in reducing postoperative SSIs in patients who undergo solid-organ transplantation.^{5–7} The Infectious Diseases Society of America (IDSA)/American Society of Health-System Pharmacists (ASHP)/Surgical Infection Society (SIS)/Society for Healthcare Epidemiology of America (SHEA) guidelines recommend a third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone for perioperative antibiotic prophylaxis in LT recipients.⁸

Liver transplant recipients, particularly those with high-risk factors such as high Model for End-Stage Liver Disease (MELD) scores, are vulnerable to developing infections with multidrug-resistant (MDR) gram-negative bacilli because of the prolonged exposure to broad-spectrum antibiotics and frequent invasive procedures.^{9–11} The increasing prevalence of multidrug resistance, such as that by extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae, has driven the increased use of carbapenems in clinical practice. However, clinicians must balance the risk of severe MDR infection with the risk of the development of carbapenem resistance. It remains inconclusive whether carbapenems can be used as surgical prophylaxis for high-risk patients who undergo LT.

The aim of this study was to compare the effectiveness of carbapenems with that of cephalosporin or piperacillin-tazobactam for perioperative antibiotic prophylaxis in high-risk LT recipients with a MELD score ≥ 30 .

Patients and Methods

Study Design and Participants

Between May 2018 and September 2020, 585 adult patients (age > 18 years) underwent their first liver-only transplantation at the First Affiliated Hospital of Zhejiang University, School of Medicine, China. Of these patients, 117 had a MELD score of ≥ 30 . From among these patients, six were excluded because they passed away within 7 days after LT and another six were excluded because they had pre-LT infections within one week before transplantation (2 patients had blood stream infections; 2 patients had peritonitis; 3 patients had chest infections and 1 patient had leg abscess). In the end, 105 LT patients had a MELD ≥ 30 and were without pre-LT infections. Perioperative antibiotic prophylaxis was administered for at least 72 h after LT. The induction immunosuppression regimen comprised basiliximab and corticosteroids and the maintenance regimen consisted of tacrolimus and mycophenolate mofetil with or without corticosteroids in the early stage after LT. Since Jan 1, 2015, organ procurement from executed prisoners had been completely ceased in China. No organs from executed prisoners were used in any case involved in this study.

Setting

The First Affiliated Hospital of Zhejiang University, School of Medicine is a 2200-bed tertiary care university hospital in Hangzhou, China. Over 3000 LTs have been performed until December 2020 at the LT center.

Data Collection and Definitions

The patients' electronic case reports were reviewed, and the following variables were evaluated: recipients' characteristics (age, sex, body mass index [BMI], MELD score, Child–Pugh score, underlying liver diseases, and pre-LT intensive care unit [ICU] stay), graft information (graft type, cold ischemia time, and warm ischemia time), procedure-related information (intraoperative blood loss, vascular complications, biliary complications, post-LT intra-abdominal bleeding, and reoperation), perioperative antibiotic prophylaxis regimens, post-LT conditions (vasopressor support, mechanical ventilation, and renal replacement therapy [RRT]), infection variables (time, location, and pathogen), and outcomes (180-day post-LT survival rate).

Infection was defined per the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) 2019 criteria.⁵ However, because this was a retrospective study, only culture-positive infections were included in this study. Patients with positive blood cultures and peritoneal fluid, biliary juice, sputum, endotracheal aspiration,

urine, and other samples according to the CDC/NHSN criteria were retrospectively evaluated by two experts to assess whether they had infections.

CRE is defined as Enterobacteriaceae that is resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase according to the Centers for Disease Control and Prevention.¹² Detection of carbapenem resistance is based Clinical and Laboratory Standards Institute (CLSI) breakpoints.¹³

Vascular complications included hepatic artery thrombosis, hepatic vein thrombosis, and portal vein thrombosis. Biliary complications included bile duct stenosis and bile leakage.

Statistical Analysis

Patients who received carbapenems as antibiotic prophylaxis were compared to those who received cephalosporin or piperacillin-tazobactam. Continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were compared using Pearson's chi-square or Fisher's exact test when appropriate. All variables with a *p*-value ≤ 0.05 in the univariate analysis were included in the logistic regression and/or Cox regression for multivariable analysis. A *p*-value ≤ 0.05 was considered significant. All statistical calculations were performed with SPSS 25.

Results

This study population consisted of 105 patients who underwent their first liver-only transplantation. Among them, 78 patients (74.3%) received non-carbapenem antibiotics for surgical prophylaxis (piperacillin-tazobactam, 21 patients; cefoperazone-sulbactam, 57 patients), while 27 patients (25.7%) received carbapenems for surgical prophylaxis (meropenem, 24 patients; imipenem-cilastatin, 3 patients). The basic characteristics of the patients in the carbapenem and non-carbapenem groups are shown in Table 1. Patients in the carbapenem group had a worse perioperative condition: higher MELD score (35.2 ± 3.9 vs 33.4 ± 3.5 ; $p = 0.030$) and higher chances of pre-transplant ICU stay (44.4% vs 21.8%; $p = 0.023$) and vasopressor support within 24 h after transplantation (29.6% vs 3.8%; $p = 0.001$). In addition, a greater percentage of patients in the carbapenem group required mechanical ventilation for more than 72 h (55.6% vs 17.9%; $p = 0.000$). The two groups showed no significant differences in the rates of surgical complications, such as intra-abdominal hemorrhage, vascular complications, biliary complications, and reoperation.

Overall, 48 (45.7%) of the 105 patients developed infections within 30 days after LT, and 24 of these 48 patients (50.0%) had polymicrobial infections. In the carbapenem group, 18 patients (66.7%) had infections within a median of 7.5 (interquartile range [IQR] 1.0–17.25) days after LT. The most common pathogen was *Enterococcus* (25.9%), followed by Enterobacteriaceae (18.5%) (Table 2). And it was common for patients to have more than one site of infection after LT: 10 patients (37.0%) had intra-abdominal infections, 7 patients (25.9%) developed bacteremia and 11 patients (40.7%) had pneumonia. In the non-carbapenem group, 30 patients (38.5%) had infections within a median of 3.0 (IQR 1.0–7.25) days after LT. Enterobacteriaceae (18.0%) was the most common pathogen, followed by *Enterococcus* (14.1%). Eighteen patients (23.1%) had intra-abdominal infections, 17 patients (21.8%) developed bacteremia and 17 patients (21.8%) had pneumonia.

Overall, 14 patients (13.3%) had CRO infections (carbapenem-resistant Enterobacteriaceae and carbapenem-resistant *Acinetobacter baumannii*, 6 patients each; carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Cupriavidus*, 1 patient each). The two groups showed no significant difference in the proportion of CRO infections (18.5% vs 11.5%; $p = 0.345$) (Table 1).

A greater percentage of patients in the carbapenem group had infections within 30 days after LT (66.7% vs 38.5%; $p = 0.011$) (Table 1). In order to analyze whether prophylactic antibiotics was an independent risk factor of post-LT infections, the risk factors for infections were assessed by univariate and multivariate analyses (Table 3). Univariate analysis suggested that the following risk factors were associated with infection within 30 days after LT: prophylaxis with carbapenems, vasopressor support within 24 h after transplantation, ventilation for >72 h, reoperation, RRT > 3 days, and a high Child–Pugh score. Multivariate analysis showed that only reoperation (OR, 3.942; 95% CI, 1.004–15.468;

Table 1 Comparison of Patients Who Did and Did Not Receive Carbapenems as Antibiotic Prophylaxis

	Carbapenem Group (n = 27)	Non-Carbapenem Group (n = 78)	p
Age (years) (media [±SD])	48.8±12.1	48.2±11.4	0.818
Sex, male	22 (81.5%)	60 (76.9%)	0.622
BMI	25.4±6.8	26.9±8.3	0.415
Pre-LT ICU stay	12 (44.4%)	17 (21.8%)	0.023
Child–Pugh Score	12.0±1.2	11.6±1.3	0.162
MELD score (media [±SD])	35.2±3.9	33.4±3.5	0.030
Underlying liver disease*			
HBV	21 (77.8%)	59 (75.6%)	0.822
HCC	0 (0%)	1 (1.2%)	1.000
Alcohol	5 (18.5%)	5 (6.4%)	0.120
AIH	0 (0%)	6 (7.7%)	0.335
PBC	0 (0%)	3 (3.8%)	0.567
Others	3 (11.1%)	12 (15.4%)	0.755
Graft type			0.382
DBD	9 (33.3%)	15 (19.2%)	
DBCD	5 (18.5%)	12 (15.4%)	
DCD	13 (48.1%)	50 (64.1%)	
Living donor	0 (0.0%)	1 (1.3%)	
Cold ischemia time (min), media (±SD)	547.5±137.7	523.4±164.4	0.528
Warm ischemia time (min), media (±SD)	9.0±11.0	10.4±9.2	0.545
Intraoperative bleeding of ≥1500 mL	15 (55.5%)	27 (34.6%)	0.056
Vasopressor support within 24 h after LT	8 (29.6%)	3 (3.8%)	0.001
Intra-abdominal hemorrhage	2 (7.4%)	4 (5.1%)	0.646
Vascular complications	0 (0%)	4 (5.1%)	0.570
Biliary complications	2 (7.4%)	7 (9.0%)	1.000
Reoperation	5 (18.5%)	11 (14.1%)	0.582
Ventilation for >72 h	15 (55.6%)	14 (17.9%)	0.000
Renal replacement therapy for >3 days	10 (37.0%)	16 (20.5%)	0.086
Infection within 30 days after LT	18 (66.7%)	30 (38.5%)	0.011
CRO infection	5 (18.5%)	9 (11.5%)	0.345

Note: *Some patients presented more than one cause of liver disease.

Abbreviations: AIH, autoimmune hepatitis; BMI, body mass index; CRO, carbapenem-resistant organism; DBD, donation after brain death; DBCD, donation after brain death followed by circulatory death; DCD, donation after circulatory death; ICU, intensive care unit; LT, liver transplantation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; SD, standard deviation.

Table 2 Bacterial Pathogens of Infections

Pathogen	Episodes			p
	Total (n = 105)	Carbapenems (n = 27)	Non-Carbapenems (n = 78)	
Enterobacteriaceae	19 (18.1%)	5 (18.5%)	14 (18.0%)	0.947
<i>Pseudomonas aeruginosa</i>	2 (1.9%)	1 (3.7%)	1 (1.3%)	0.428
<i>Acinetobacter baumannii</i>	10 (9.5%)	3 (11.1%)	7 (9.0%)	0.744
<i>Stenotrophomonas maltophilia</i>	8 (7.6%)	5 (18.5%)	3 (3.9%)	0.013
<i>Burkholderia</i> spp.	7 (6.7%)	2 (7.4%)	5 (6.4%)	0.858
<i>Enterococcus</i> spp.	18 (17.1%)	7 (25.9%)	11 (14.1%)	0.160
Others	12 (11.4%)	1 (3.7%)	10 (12.8%)	0.182

p = 0.049) and a high Child–Pugh score (OR, 1.726; 95% CI, 1.183–2.519; p = 0.005) were independent risk factors for infections. Prophylaxis with or without carbapenems was not an independent risk factor for infections within 30 days after LT (OR, 1.940, 95% CI, 0.638–5.898, p = 0.243).

Table 3 Univariate and Multivariate Analyses of Risk Factors for Infections After Liver Transplantation

Risk Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Prophylaxis with carbapenems	3.200	1.274–8.038	0.013	1.940	0.638–5.898	0.243
MELD score	1.093	0.982–1.216	0.103	NS	NS	NS
Intraoperative bleeding of ≥ 1500 mL	1.333	0.609–2.921	0.472	NS	NS	NS
Vasopressor support within 24 h after LT	14.737	1.811–119.923	0.012	6.352	0.631–63.918	0.117
Ventilation for >72 h	3.810	1.527–9.406	0.004	0.972	0.297–3.184	0.963
Reoperation	4.417	1.319–14.784	0.016	3.942	1.004–15.468	0.049
Biliary complications	0.945	0.239–3.738	0.936	NS	NS	NS
Vascular complications	3.733	0.375–37.123	0.261	NS	NS	NS
Renal replacement therapy for >3 days	2.925	1.159–7.380	0.023	1.871	0.618–5.666	0.268
Pre-transplant ICU stay	2.056	0.862–4.904	0.104	NS	NS	NS
Child–Pugh score	1.739	1.248–2.422	0.001	1.726	1.183–2.519	0.005
Intra-abdominal bleeding	2.500	0.437–14.287	0.303	NS	NS	NS

Abbreviations: CI, confidence interval; ICU, intensive care unit; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NS, not significant; OR, odds ratio.

The 180-day survival rate of patients who underwent LT with MELD ≥ 30 was 81.9% in this study. The 180-day survival rates of patients in the carbapenem and non-carbapenem groups were 74.1% and 84.6%, respectively ($p = 0.238$) (Figure 1). We further analyzed the risk factors for 180-day survival after LT by Cox regression, and the results of this analysis are shown in Table 4. Univariate analysis suggested that five risk factors were associated with 180-day survival after LT, including the MELD score, vascular complications, RRT > 3 days, intra-abdominal bleeding, and CRO infection. Multivariate analysis identified four independent risk factors associated with 180-day survival post-LT, namely, MELD score (HR, 1.216; 95% CI, 1.040–1.422; $p = 0.014$), vascular complications (HR, 9.302; 95% CI, 1.769–48.914; $p = 0.008$), intra-abdominal bleeding (HR, 9.056; 95% CI, 2.185–37.541; $p = 0.002$), and CRO infection (HR, 6.669; 95% CI, 2.248–19.788; $p = 0.001$). Prophylaxis with or without carbapenems was not associated with the 180-day survival after LT. Regarding the cause of death, 9 patients (47.4%) died of infection. And 4 of the 9 patients had CRO infections.

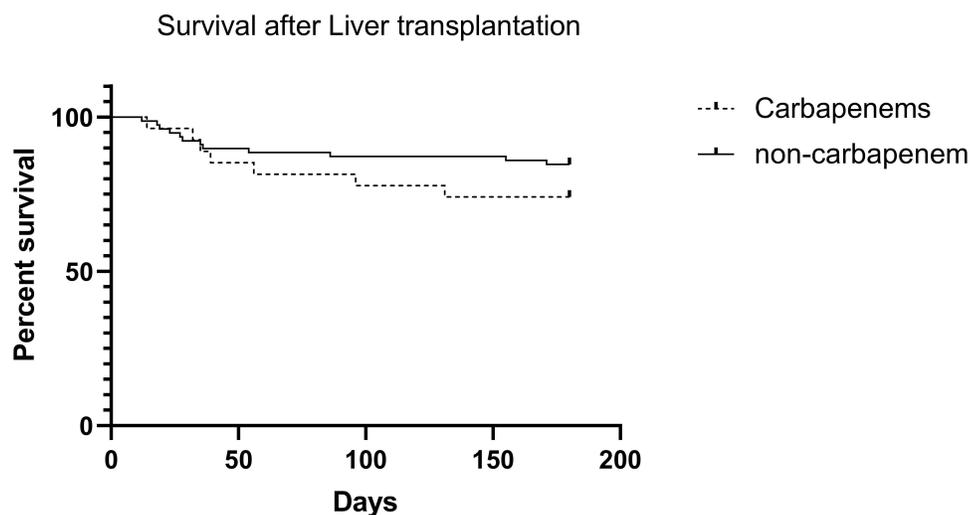


Figure 1 The 180-day post-transplant survival rate in patients who received carbapenems and those who received non-carbapenems for surgical prophylaxis (74.1% and 84.6%, log-rank $p = 0.238$).

Table 4 Factors Associated with 180 Days of Survival in Patients After Liver Transplantation in the Cox Model

Risk Factor	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Prophylaxis with carbapenems	1.741	0.685–4.424	0.244	NS	NS	NS
MELD score	1.163	1.034–1.309	0.012	1.216	1.040–1.422	0.014
Intraoperative bleeding of ≥ 1500 mL	0.884	0.348–2.246	0.796	NS	NS	NS
Vasopressor support within 24 h after LT	1.699	0.495–5.832	0.4	NS	NS	NS
Ventilation for >72 h	2.135	0.859–5.311	0.103	NS	NS	NS
Biliary complications	0.547	0.073–4.097	0.557	NS	NS	NS
Vascular complications	4.521	1.040–19.655	0.044	9.302	1.769–48.914	0.008
Renal replacement therapy for >3 days	3.926	1.592–9.677	0.003	2.119	0.792–5.672	0.135
Pre-transplant ICU stay	1.654	0.651–4.203	0.29	NS	NS	NS
Child–Pugh score	1.363	0.951–1.955	0.092	NS	NS	NS
Intra-abdominal bleeding	3.936	1.144–13.542	0.03	9.056	2.185–37.541	0.002
Infection within 30 days after LT	2.249	0.885–5.715	0.089	NS	NS	NS
CRO infection	3.671	1.390–9.696	0.009	6.669	2.248–19.788	0.001

Abbreviations: CRO, carbapenem-resistant organism; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NS, not significant.

Discussion

Postoperative infections occur in up to 8–38% of LT patients, and are related to the patients' poor nutritional status, comorbidities, the complexity of the surgical procedure, which requires penetration of the hepatobiliary system, and the use of immunosuppression.^{2,14,15} Antibiotic prophylaxis in solid organ transplantation has been described in a few studies.^{16–18} However, the benefits and disadvantages of prophylactic regimens in LT patients remain unclear because of inadequate evidence from current clinical trials.¹⁴ The optimal prophylactic antibiotic regimens should account for the risk factors of patients and local antibiotic resistance patterns. Transplant recipients with a high MELD score have additional risk factors such as poor underlying conditions, invasive procedures and use of catheters, exposure to broad-spectrum antibiotics, and colonization with MDR organisms. Moreover, according to the China Antimicrobial Surveillance Network (CHINET) 2018 report, the resistance rate of *E. coli* to piperacillin-tazobactam was 3.8–10.3%, and the resistance rate of *K. pneumoniae* to piperacillin-tazobactam was 28.7%–62%.¹⁹ On the basis of this background, we designed this study to determine whether carbapenems could be used for surgical prophylaxis to decrease the infection rate in LT recipients with a MELD score ≥ 30 .

Our study included patients with a MELD score ≥ 30 who had undergone first-time liver-only transplantation, and we found that the overall incidence of infection was 45.7% within 30 days after LT. The incidence of infections was 66.7% in the carbapenem group and 38.5% in the non-carbapenem group. However, this difference may not be directly associated with antibiotic prophylaxis regimens because clinicians tend to prescribe carbapenems to patients with worse clinical conditions. And this was an important bias that might affect results. Therefore, we performed multivariate analyses and found out that only reoperation and the Child–Pugh score were independent risk factors for infections within 30 days after LT. Other studies have demonstrated that a prolonged ICU or hospital stay, high MELD scores, requirement of >4 units of red blood cells in the surgery, anastomotic leakage, donor infection, and post-transplant RRT were also risk factors for infections in LT.^{15,20} Some studies have suggested that prophylactic antibiotics may affect the incidence of SSIs in transplant recipients.^{16,17} However, none of these studies evaluated carbapenems as surgical prophylaxis in LT patients.

Liver transplant recipients are particularly vulnerable to developing CRO infection. The incidence of post-LT CRE infection varies among different centers, from 3% to 23%.^{21–23} In our previous study, the incidence of CRE infection was 6.7% within 30 days after LT, and patients with CRE infections had significantly lower 180-day survival rates (51.5% vs 92.4%, $p < 0.001$).²⁴ Since the use of carbapenems is associated with an increased risk of CRO infection, we analyzed the incidence of CRO infection in this study.²⁵ We found that 13.3% of patients developed CRO infections within 30 days

after LT. And, the CRO infection rate did not differ significantly between the carbapenem and non-carbapenem groups. However, in our study, the number of CRO infection was relatively small to draw firm conclusions.

Finally, we found that the MELD score, vascular complications, intra-abdominal bleeding, and CRO infection were independent risk factors associated with the 180-day post-LT survival. Prophylaxis with carbapenems was not one of these factors, probably because cephalosporin or piperacillin-tazobactam was adequate to cover most pathogens and carbapenems would not further decrease the incidence of infection. Moreover, in this study, we did not observe an association between the use of carbapenems and CRO infection, which was one risk factor of post-LT survival.

Our study had some limitations. First, it was a monocentric retrospective study. Thus, our data may vary from the findings obtained at other centers. Moreover, we focused on culture-positive infection, which may have underestimated the overall incidence of infections. Second, the size of this study is relatively small; therefore, we were unable to perform subgroup analysis to determine whether highly selected patients may benefit from carbapenems. Third, this study did not include variable about MDR colonization prior to LT, which is a known risk factor of post-LT infections and could affect the prophylaxis selection, because we did not routinely screen LT candidates before LT.

Conclusion

We found that reoperation and the Child–Pugh score were independent risk factors for infections within 30 days after LT. Moreover, the MELD score, vascular complications, intra-abdominal bleeding, and CRO infection were independent risk factors for survival 180 days post-LT. The use of carbapenems for surgical prophylaxis was not associated with post-LT infection or survival. In this study, the use of carbapenems was not associated with CRO infection as well. Therefore, carbapenems are not superior to cephalosporin or piperacillin-tazobactam as perioperative antibiotic prophylaxis in liver transplantation recipients with a MELD score ≥ 30 . The complexities of the clinical situation of individual LT patients will necessitate thoughtful prophylactic regimens. High-quality studies are needed to build a proper risk-stratification system to help guide the choice of prophylactic antibiotics.

Ethics Approval

This study complied with the guidelines of the Chinese Ethics Committee and the Declaration of Helsinki and was approved by the research ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT20220045A). All organs were donated voluntarily with written informed consent, and the organ donations were conducted in accordance with the Declaration of Istanbul. The data were anonymous, and the requirement for informed consent was waived for our retrospective study. Since Jan 1, 2015, organ procurement from executed prisoners had been completely ceased in China. No organs from executed prisoners were used in any case involved in this study.

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Disclosure

The authors report no conflicts of interest for this work and declare that there is no competing interest regarding the publication of this paper.

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