

Clinical Communications

Impact of beta-lactam allergy label in liver transplant recipients

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Clinical Implications

- Self-reported beta-lactam allergy is associated with worse clinical outcomes. However, this association was not present in our cohort of liver transplant recipients with a beta-lactam allergy label.

Approximately 10% of patients report penicillin allergy, but less than 1% of these patients are found to be truly allergic after an allergy evaluation.¹ Patients with a beta-lactam allergy label (BLAL) are associated with suboptimal antibiotic therapy, extended length of stay (LOS), increased readmission rates, and complications from antimicrobials.² The impact of BLAL in solid-organ transplant recipients remains mostly unknown.³ Liver transplant recipients (LTRs) are an important population for study because patients with end-stage liver disease suffer from high rates of infectious complications. The objective of this study was to determine the impact of BLAL among LTRs.

We collected demographic and clinical data through the review of electronic medical records for all LTRs at our institution from January 1, 2006, to December 31, 2016. This study was approved by our institutional review board. We included patients 18 years or older who underwent liver transplantation. We excluded patients who received a second transplantation within the first 100 days, recipients of dual organs (eg, liver-kidney), patients who received beta-lactams during liver transplantation without an adverse reaction in spite of a BLAL in the chart, or missing clinical data. The primary outcome was a composite measure of LOS, 30-day readmission rate, and 30- and 360-day mortality. Secondary outcomes included organ-space surgical-site infections (SSIs) at 30 days, *Clostridium difficile* infection (CDI) at 1 year, and colonization or infection by extended-spectrum beta-lactamase-producing Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, or vancomycin-resistant *Enterococcus*.

We performed a 2:1 propensity match. The propensity score was constructed using a logistic regression analysis with allergies as the outcome. The variables used in the propensity score were sex, liver diagnosis groups, intraoperative continuous renal replacement therapy, year of transplant, age at diagnosis, donor risk index, operative time, blood loss, raw model of end-stage liver disease, and donation after circulatory death. Continuous variables were compared between the groups using Wilcoxon rank-sum tests. Categorical variables were compared using χ^2 tests.

Of 1809 included LTRs, 87 (4.8%) had a BLAL (age median, 58 years; 51.7% males) (Table I). A total of 174 LTRs were

matched as controls. We excluded 31 LTRs with BLAL who received SSI prophylaxis with a cephalosporin without previous testing (28 received cefotaxime and 3 ceftriaxone); none of the patients exhibited immediate hypersensitivity reactions. There were no differences in mortality within the first month after transplant. Patients with a BLAL showed a trend toward increased mortality during the first year compared with patients without a label (8.0% vs. 4.0%, respectively; $P = .17$) as well as an extended LOS (8.0 vs. 7.0 days, respectively, $P = .16$). Thirty-day readmission rates posttransplantation and rates of colonization or infection by multi-drug-resistant organisms (MDROs) and CDI were similar in both groups (Table I). Organ-space SSI at 30 days in patients with BLAL was not statistically different from that in the control group (5.7% vs. 10.3%, respectively; $P = .22$).

Among the 62 LTRs who were readmitted in the first 30 days (Table I), 20 patients in the BLAL group were readmitted for multiple complaints from which 6 had a positive culture. In the control group, 42 were readmitted from which 24 patients had a microorganism isolated in the culture (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). On comparing SSI prophylaxis (Table II), it was found that 88.5% of patients with BLAL received prophylaxis with a monobactam plus glycopeptide whereas 97% of controls received a cephalosporin ($P \leq .001$). There were no adverse reactions reported in the 78 patients who received monobactam plus glycopeptide antibiotics.

In this retrospective review of 87 LTR cases with BLAL using a 2:1 match to LTR controls over 11 years at our tertiary care center, we found no statistically significant differences in clinical outcomes among the groups. However, there was a trend in increasing mortality during the first year after transplant and LOS in patients with a BLAL compared with controls.

A BLAL was previously reported between 12% and 16% of patients undergoing solid and hematopoietic cell transplantation.^{4,5} We found a lower prevalence of patients with a BLAL (5%) in our cohort, which may be explained by the presence of an allergy clinic, which actively confirms or discards the existence of a penicillin allergy in transplant candidates,⁶ and by the exclusion of LTRs who received a penicillin-based prophylaxis during liver transplantation without an adverse reaction in spite of a BLAL.

Our study did not find significant differences in mortality, LOS, or readmission rates in LTRs with a BLAL compared with controls, which is similar to a previous report.⁵ Khumra et al⁴ described similar findings in a small retrospective cohort but reported an increasing trend in the number of isolated multi-drug-resistant Gram-negative bacteria and CDI.⁴

Increased use of broad-spectrum antibiotics has been associated with worse clinical outcomes, including a higher risk of therapeutic failure,⁷ and colonization or infection by MDROs.⁸ In our cohort, there was an increased use of broad-spectrum antibiotics among patients with a BLAL, which is similar to another study.⁴ However, this use of broad-spectrum antibiotics for SSI did not affect outcomes. Perioperative prophylaxis in LTRs with BLAL in our institution includes the combination of a monobactam and a glycopeptide. Although we did not find

TABLE I. Characteristics of LTRs with a penicillin allergy label and controls without a penicillin allergy label

Characteristic	Penicillin allergy label	Controls	Total	P value
Age (y), median (IQR)	58 (51-66)	58 (49-64)	58 (50-65)	.49
Sex: male	45 (51.7)	92 (52.9)	137 (52.5)	.86
Indication for liver transplant				.13
Alcoholic cirrhosis	16 (18.4)	37 (21.3)	53 (20.3)	
Nonalcoholic steatohepatitis	20 (23.0)	31 (17.8)	51 (19.5)	
Hepatitis C	22 (25.3)	34 (19.5)	56 (21.5)	
Hepatitis B	0 (0.0)	3 (1.7)	3 (1.1)	
Autoimmune hepatitis	7 (8.0)	7 (4.0)	14 (5.4)	
Cholestatic causes	5 (5.7)	29 (16.7)	34 (13.0)	
Malignancy	0 (0.0)	2 (1.1)	2 (0.8)	
Cryptogenic	9 (10.3)	20 (11.5)	29 (11.1)	
Other	7 (8.0)	11 (6.3)	18 (6.9)	
MELD score, median (IQR)	18 (13-24)	18 (12-24)	18 (13-24)	.58
PRBC (mL), median (IQR)	2800 (1750-4200)	2800(1750- 4550)	2800 (1750- 4550)	.58
Intraoperative CRRT	9 (10.3)	15 (8.6)	24 (9.2)	.65
Operation time (min), median (IQR)	234.0 (191-289)	233.5 (190.0-288.0)	234.0 (191.0-288.0)	.96
Donation after circulatory death	13 (14.9)	24 (13.8)	37 (14.2)	.80
Donor Risk Index, median (IQR)	1.7 (1.2-2.0)	1.6 (1.3-2.1)	1.7 (1.3-2.0)	.69
LOS, median (IQR)	8.0 (6-13)	7.0 (6-11)	8.0 (6-11)	.16
Readmission within 30 d from transplant	20 (23.0)	42 (24.1)	62 (23.8)	.84
Mortality 30 d after liver transplantation	1 (1.1)	3 (1.7)	4 (1.5)	.72
Mortality 1 y after liver transplantation	7 (8.0)	7 (4.0)	14 (5.4)	.17
Organ-space SSI within 30 d after surgery	5 (5.7)	18 (10.3)	23 (8.8)	.22
CDI within 1 y from transplant	5 (5.7)	8 (4.6)	13 (5.0)	.69
ESBL colonization	2 (2.3)	4 (2.3)	6 (2.3)	>.99
ESBL infection	2 (2.3)	5 (2.9)	7 (2.7)	.79
MRSA colonization	2 (2.3)	3 (1.7)	5 (1.9)	.75
MRSA infection	1 (1.1)	3 (1.7)	4 (1.5)	.72

CCRT, Continuous renal replacement therapy; ESBL, extended-spectrum beta-lactamases; IQR, interquartile range, MELD score, model of end-stage liver disease score; MRSA, methicillin-resistant *Staphylococcus aureus*; PRBC, intraoperative transfusion of packed red blood cells.

Values are n (%) unless otherwise indicated.

TABLE II. SSI prophylaxis in LTRs

Prophylactic antibiotic	Penicillin allergy label	Controls	Total	P value
Monobactams + glycopeptide				
Aztreonam + vancomycin	77 (88.5)	1 (0.6)	78 (29.9)	≤.001
Cephalosporins				
Cefazolin	0 (0.0)	1 (0.6)	1 (0.4)	
Cefepime	0 (0.0)	2 (1.1)	2 (0.8)	
Cefotaxime	0 (0.0)	149 (85.6)	149 (60.1)	
Ceftizoxime	0 (0.0)	14 (8.0)	14 (5.4)	
Ceftriaxone	0 (0.0)	4 (2.3)	4 (1.5)	
Quinolones				
Levofloxacin	6 (6.9)	1 (0.6)	7 (2.7)	
Others*	4 (4.6)	3 (1.7)	7 (2.7)	

Values are n (%).

*Others: Linezolid or meropenem.

statistically significant differences in infection or colonization by MDROs or CDI in patients with a BLAL, a comprehensive evaluation of these patients by an allergist combined with an antimicrobial stewardship program has been proposed as a rational approach to reducing the risk of antimicrobial resistance and CDI.⁹

The limitations of this study include its retrospective nature and the small sample size in a single center, which could mean the results may not be generalizable to LTRs elsewhere.

In our cohort, BLAL did not impact mortality, LOS, or readmissions in LTR. Further larger studies are needed to examine clinical outcomes in patients with beta-lactam allergy in

LTR. Our study was associated with an increased use of broad-spectrum antibiotics. Consequently, it is likely that antimicrobial resistance and health care costs may increase due to suboptimal antimicrobial therapy. We recommend penicillin allergy delabeling tactics, which improve antimicrobial stewardship. Furthermore, future prospective studies should focus on the outcomes of patients undergoing transplantation with a BLAL.

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ONLINE REPOSITORY

TABLE E1. Microbiological profile of patients readmitted within 30 d from transplant *

Microorganism	Penicillin allergy label (n=6)	Culture type	Controls (n=24)	Culture type
<i>Proteus mirabilis</i>	1	Peritoneal fluid		
<i>Escherichia coli</i>	1	Abdominal wall abscess	1	Urine
<i>Klebsiella pneumoniae</i>			4	Blood (3), urine (1)
<i>Klebsiella oxytoca</i>	1	Surgical wound	1	Urine
<i>Pseudomonas aeruginosa</i>			1	Urine
<i>Enterobacter cloacae</i>			1	Urine
<i>Enterobacter aerogenes</i>			1	Urine
<i>Enterococcus faecium</i>			1	Peritoneal fluid
<i>Enterococcus faecalis</i>	1	Blood	2	Peritoneal fluid (1), blood (1)
<i>Staphylococcus aureus</i>			1	Blood
<i>Enterococcus raffinosus</i>	1	Blood		
CoNS			4	Peritoneal fluid (2), liver biopsy (1), urine (1)
VRE			4	Blood (1), peritoneal fluid (2), native liver biopsy (1)
MRSA			2	Blood (1), peritoneal fluid (1)
<i>Candida tropicalis</i>			1	Cerebrospinal fluid
Non-albicans <i>Candida</i> spp				

CoNS, Coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococcus.

*A total of 62 LTRs were readmitted in the first 30 d; 20 patients in the BLAL group were readmitted for multiple complaints from which 6 had a positive culture. In the control group, 42 were readmitted, from which 24 had a microorganism isolated in the culture.