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Bacterial infection monitoring in the early period after liver transplantation

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Purpose: Infection remains the main cause of morbidity and mortality in liver transplantation (LT) recipients; however infection is notoriously difficult to diagnose because its usual signs and symptoms of infection may be masked or absent. This study comprises an analysis of bacterial infections in the early period after LT.
Methods: This is a study of 129 adults who underwent LT from January 2013 to December 2013, and it includes patients who were followed daily from the day of transplantation to 1-week posttransplantation using bacteriological cultures of blood, urine, sputum, and drained ascites.
Results: The following factors were significantly different between the positive and negative culture groups: living donor LT *vs*. deceased donor LT (odds ratio [OR], 3.269; P = 0.003), model for end-stage liver disease score (OR, 4.364; P < 0.001), and Child-Pugh classification (P = 0.007). Neither positive culture nor negative culture was associated with infection within 4 weeks of surgery (P = 0.03), and most events were due to surgical complications (75%).
Conclusion: Since the full effect of immunosuppression is not yet present during the first month after LT, we suggest that the number of bacterial culture test could be reduced such that they are performed every other day depending on patient's situation.
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Key Words: Culture techniques, Infection, Liver transplantation

INTRODUCTION

Liver transplantation (LT) has become an established treatment for properly selected patients with end stage liver disease, primary and some secondary hepatic malignancies and some rare metabolic liver diseases. Increased use of potent immunosuppressive agents has dramatically reduced the incidence of rejection in the transplant population, while increasing patient susceptibility to opportunistic infections and cancer [1]. Infection and rejection remain the major causes of

morbidity after LT, together accounting for up to 85% of deaths [2].

Many studies have reported that infection is one of the main factors influencing morbidity and mortality in posttransplant patients. Approximately 80% of solid-organ transplant recipients suffer at least one significant episode of infection during the first year following transplantation [3]. Most of the infections have a bacterial etiology and they occur early after transplantation [4,5]. Infections in this patient population are notoriously difficult to diagnose because their usual signs and

symptoms, such as fever and leukocytosis, may be masked or absent. Mild infections are dangerous in immunosuppressed patients [6].

An investigation of the methods useful for early detection of hidden infections is needed. Kim et al. [7] reported that periodic microbiologic surveillance is useful for predicting posttransplantation pneumonia and intra-abdominal infection.

This study comprises an analysis of bacterial infections that occur during the early period after LT in adults. Laboratory culture tests were performed every day and the results were analyzed to determine if an analysis can improve the detection of early infections.

METHODS

This study included 129 adults who underwent LT from January 2013 to December 2013 at a single center institution. These patients had no symptoms or signs of infection before transplantation. Blood, urine, and sputum cultures were collected from patients the day before transplantation, and there was no evidence of infection. Bacterial cultures were performed every day from the day of transplantation to 1 week after LT. Samples of blood, urine, sputum, and drained ascites were collected for culture and identification of the isolated microorganisms. Cultures and microorganism identification were conducted in accordance with standard microbiological procedures [8].

In this study, cultures harboring bacteria were identified as positive cultures, while cultures that did not contain bacteria were identified as negative cultures. In addition, after the operation, infection was defined as the occurrence of fever above 38°C, use of antibiotics, positive culture and a sudden increase in leukocyte count or C-reactive protein level to 2–3 times the upper limit of normal.

Antimicrobial prophylaxis

All patients routinely received prophylaxis for antibacterial, protozoal, and fungal infections after LT. Perioperative anti-microbial prophylaxis consisted of cefotaxime (3 g/day, IV) and ampicillin/sulbactam (12 g/day, intravenous [IV]) for 3 days. Pneumocystis pneumonia prophylaxis consisted of trimethoprim/sulfamethoxazole (80 mg/400 mg, oral) from the time of the operation to 6 months after LT. To prevent fungal infections, itraconazole (100 mg, oral) was given twice a day for one month after LT.

Table 1. Demographic and clinical characteristics of liver transplantation recipients

Characteristic	Culture positive (n = 35)	Culture negative (n = 94)	OR (95% CI)	P-value
Age (yr)	54.4 ± 10.4	52.5 ± 9.3		0.319
Sex			1.81 (0.76–4.33)	0.180
Male	24 (68.6)	75 (79.8)		
Female	11 (31.4)	19 (20.2)		
Diabetes mellitus	4 (11.4)	24 (25.5)	0.38 (0.12–1.18)	0.084
Hypertension	3 (8.6)	13 (13.8)	0.58 (0.16–2.19)	0.555
Underlying liver disease			-	0.375
Alcoholic	4 (11.4)	6 (6.4)		
Viral hepatitis				
B	23 (65.7)	72 (76.6)		
C	3 (8.6)	9 (9.6)		
B & C	0 (0)	1 (1.1)		
Autoimmune	1 (2.9)	1 (1.1)		
Drug-related	2 (5.7)	1 (1.1)		
Cryptogenic	2 (5.7)	4 (4.3)		
Type of transplantation			3.27 (1.45–7.37)	0.003
LDLT	17 (48.6)	71 (75.5)		
DDLT	18 (51.4)	23 (24.5)		
MELD	25.97 ± 14.76	16.81 ± 10.1	4.36 (1.92–9.93)	
<20	15 (42.9)	72 (72.6)		0.001
>20	20 (57.1)	22 (23.4)		<0.001
Child-Turcott-Pugh			2.71 (1.22–6.00)	0.013
A & B	15 (42.9)	63 (67.0)		
C	20 (57.1)	31 (33.0)		

Values are presented as mean ± standard deviation or number (%).
OR, odds ratio; CI, confidence interval; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; MELD, model for end-stage liver disease.

Immunosuppression

In our center, immunosuppression was accomplished as previously described [9]. Basiliximab (20 mg) was used as an induction agent in all recipients during LT and on day 4 after LT. Patients were infused with prostaglandin E1, gabexate mesilate, and methylprednisolone. Maintenance immunosuppressive therapy consisted of corticosteroids, tacrolimus, and mycophenolate mofetil (MMF). Corticosteroids were withdrawn at 3 months after transplantation. Tacrolimus treatment was initiated on postoperative day 3, and the optimal blood level was adjusted to maintain a trough plasma concentration of 10 ng/mL during the first month (it was reduced to 5–8 ng/mL after the first month). Beginning on postoperative day one, 750 mg of MMF was administered twice a day.

Statistical analysis

Student t-test was used to analyze continuous variables, and the chi-square test or Fisher exact test was used to analyze categorical variables. We analyzed the risk factors linked with bacteremia by univariate and multivariate logistic regression analyses. Statistical analysis was performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) and P-values less than 0.05 were statistically significant.
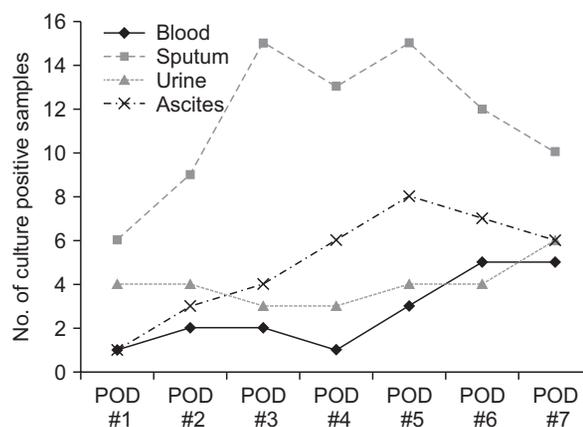
RESULTS

Among the 129 LT recipients, 99 (76.7%) were men and 30 (23.3%) were women. Eighty-eight patients (68.2%) received living donor LT (LDLT), and 41 patients (31.8%) received deceased donor LT (DDLT). The model for end-stage liver disease (MELD) score of 87 patients (67.4%) was less than 20 points, and the MELD score of 42 patients (32.6%) was more than 20 points. Forty-seven patients (36.4%) were classified as Child-Pugh Class A, 31 (24%) were B, and 51 (39.5%) were C. Thirty-five patients (27.1%) had positive cultures, and 94 patients (72.9%) had negative cultures (Table 1). The following factors were significantly different between the positive and negative culture groups: LDLT vs. DDLT (odds ratio [OR], 3.269; 95% confidence interval [CI], 1.45–7.37; P = 0.003), MELD score (OR, 4.364; 95% CI, 1.92–9.93; P < 0.001), and Child-Pugh classification (OR, 2.71; 95% CI, 1.22–6.00; P = 0.007).

Of 129 patients, 30 patients had at least one positive preoperative blood, urine, and sputum culture, and 26 patients had antibiotics before the transplantation. Fourteen patients received LDLT and 16 patients received DDLT. The most common cause was spontaneous bacterial peritonitis in 11 patients followed by urinary tract infection in 3 patients, bacteremia in 2 patients, pneumonia in 2 patients and other infections in 8 patients. Fourteen had a negative culture for 1 week after LT, and 16 patients had a positive culture.

Table 2 shows the types of bacteria detected in positive cultures. More than 1 type of bacteria were detected in 1 patient.

Fig. 1 shows the number of positive culture samples. The results of blood, urine, sputum, and ascites culture performed for 1 week after LT are presented. Sputum culture was more

Table 2. Bacterial and fungal strains in the first week after liver transplantation

Bacterial strain	Blood	Sputum	Urine	Ascites
Gram positive bacteria				
MRSA	1	10	-	-
Staphylococcus epidermidis	1	-	-	-
Coagulase negative staphylococci	-	-	-	1
VRE	3	-	-	2
Enterococcus faecium	-	1	-	2
Enterococcus faecalis	-	-	1	-
Gram negative bacteria				
Chryseobacterium meningosepticum	-	1	-	-
Escherichia coli	-	1	2	-
Escherichia coli (ESBL)	1	-	1	-
Escherichia coli (CRGNB)	-	-	-	1
Enterobacter cloacae	-	2	-	-
Klebsiella pneumoniae	-	1	-	-
Klebsiella pneumonia (ESBL)	1	2	-	1
Klebsiella pneumonia (CRGNB)	1	-	-	-
Pseudomonas aeruginosa	-	2	-	2
Pseudomonas aeruginosa (CRGNB)	-	-	-	1
Acinetobacter baumannii	1	2	-	-
Stenotrophomonas maltophilia	-	4	-	-
Burkholderia cepacia	-	1	-	-
Fungus				
Candida	1	-	5	1
Aspergillus	-	1	-	-

ESBL, extended-spectrum beta-lactamases; CRGNB, carbapenem-resistant gram-negative bacilli.

Fig. 1. Number of culture positive samples. POD, postoperative day.
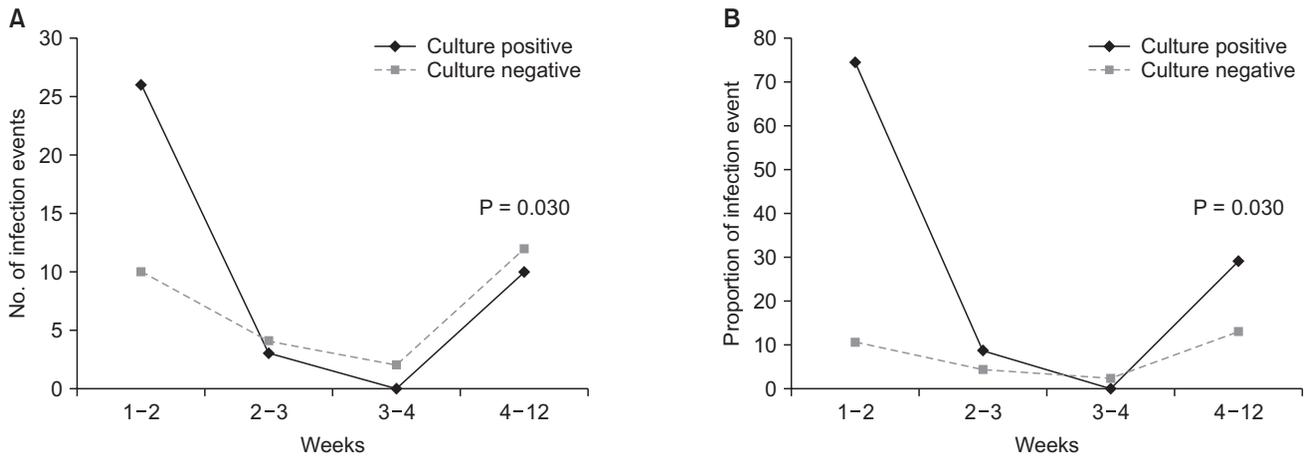
Fig. 2. (A) Infection events occurring between culture positive and culture negative. (B) Proportion of infection event after liver transplantation.

likely to be positive than any other kind of culture.

Fig. 2 shows the incidence (panel A) and proportion (panel B) of infections occurring up to 12 weeks after LT. In cultures performed within 1 week of LT, there was a statistically significant difference in the incidence rate between the positive culture group and the negative culture group at 1–2 weeks, but the occurrence of infection decreased within 4 weeks and the incidence increased again from 4 weeks to 12 weeks. Since patients are normally discharged after 3 weeks, it is not clear whether infections occurring after 4 weeks are linked with a positive culture obtained within the first week after LT. This is evident in Table 3. The incidence of infection at 4–12 weeks was higher in the positive culture group than the negative culture group (n = 12 [28.6%] *vs.* n = 10 [12.8%]), and most infections in both groups were associated with surgical complications (83% *vs.* 73%). Also, cholangitis caused by biliary stricture occurred more frequently in the negative culture group.

DISCUSSION

In this study, statistically significant differences between the positive culture group and the negative culture group were noted in LDLT and DDLT, MELD score, and Child-Pugh classification. However, the number of patients with positive and negative cultures within the first week after transplantation did not affect the number of infections within 1 month. Even though bacteria were most commonly seen in sputum samples in this study, surgical complications (biliary stricture or bile leakage) were more common sources of infection than was pneumonia after 4 weeks.

LT recipients are generally given immunosuppressants. Also, pretransplant conditions are variable and some factors cannot be controlled. Uncontrolled pretransplant variables such as underlying liver disease, lymphocyte mismatch, and a history

Table 3. Causes of infection at 4–12 weeks after liver transplantation

Cause of infection	Culture negative (n = 12, 12.8%)	Culture positive (n = 10, 28.6%)
Surgical complication	10 (83.3)	7 (70.0)
Biliary stricture	5	2
Minor bile leakage	5	5
Pneumonia	0 (0)	2 (20.0)
Urinary tract infection	1 (8.3)	1 (10.0)
Sepsis	1 (8.3)	0 (0)

of surgery may be associated with posttransplant conditions such as the presence of infectious and noninfectious diseases. These pre- and posttransplant conditions affect posttransplant management and length of stay in intensive care unit and hospital. A pretransplant MELD score of more than 25 was linked with patient and graft survival [10]. A high MELD score was indicative of a poor outcome. Our data revealed that 6 of the spontaneous bacterial peritonitis and 2 of the bacteremia were detected preoperative culture in DDLT patient and that patients with positive cultures tended to have higher MELD scores than those with negative cultures. This, suggests that patients who receive DDLT and have a high MELD score are more susceptible to infection during the preoperative period and within the first week after LT.

Posttransplant infections occurring after 1 month of surgery are primarily attributable to surgical and technical complexity, wound infection, urinary tract infection, catheter-related infection, and pneumonia [11]. Opportunistic infections are generally uncommon during the early period after transplantation, since the full effect of immunosuppression is not reached surgery-related infection is most common in the early period after LT. Our data revealed that both the positive and negative culture

groups after LT experienced a gradual decrease in the number of infection events. Therefore, it is important to consider the number of cultures immediately after LT in patients without any evidence of pretransplantation infection. However, in patients with a high MELD score, who receive DDLT, and who develop infectious episodes in the pretransplant period, it is dangerous to reduce the number of serial culture tests for infection monitoring.

A limitation of our study is a retrospective study that included small number of LT patients. Another limitation of our study is that we could not identify the operational events and techniques that may have influenced surgical complications because of the retrospective nature of the study design. We also could not evaluate the biliary complexes in living donors compared to those in deceased donors. The biliary system could be a critical factor in biliary complications other than infection. A future large prospective study could provide more informative data.

In conclusion, we suggest reducing the number of culture tests performed in patients immediately after LT because full immune suppression is not reached and bacterial culture results at 1 week after LT are unlikely to be linked to infection. However, in patients with high MELD scores, who receive DDLT, or who have evidence of preoperative infection, the option of reducing the number of culture test should be seriously reconsidered.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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