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Spectrum of Early- and Late-Onset Bacteremia after Liver Transplantation: Implications for Management

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Abstract

Bacteremia is a significant cause of morbidity and mortality after liver transplantation. Characterizing the microbiologic spectrum of bacteremia after liver transplantation may guide the initial empiric antimicrobial therapy in patients presenting with sepsis. The clinical and microbiology records of patients who received liver transplantation from January 1997 to March 2006 were reviewed. Of the 737 liver recipients, 123 (16.7%) developed bacteremia during the median follow-up period of 5.8 years (interquartile range = 2.5–8.8 years); 92 patients (12.5%) had Gram-positive bacteremia (GPB) while 47 (6.4%) had Gram-negative bacteremia (GNB). Nosocomial bacteremia was significantly more frequent among patients with early-onset compared to late-onset GPB (67% vs. 24%, $P<0.001$) and late-onset GNB (71% vs. 20%, $P=0.001$). Peritonitis (33% vs. 8%, $P=0.004$) and wound infections (13% vs. 0%, $P=0.04$) as sources were more common in early-onset compared to late-onset GPB. Likewise, peritonitis (41% vs. 7%, $P=0.007$) was more common source of early-onset compared to late-onset GNB. *Staphylococcus aureus* and *Enterococcus faecium* were the most common pathogens of early-onset GPB, while *Enterococcus faecalis* and *Streptococcus* specie were most common in late-onset GPB. *Pseudomonas aeruginosa* and anaerobes were the most common pathogens in early-onset, while *Escherichia coli* was the most common in late-onset GNB. In conclusion, the microbiologic spectrum differs between early- and late-onset bacteremia, and this should be considered in determining the initial empiric treatment of suspected bacteremias in liver transplant recipients.

Keywords

Gram-positive cocci; Gram-negative bacilli; bacteremia; sepsis; liver transplantation

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Infectious diseases are important causes of morbidity and mortality in solid organ transplant (SOT) recipients. While potent immunosuppressive agents have dramatically reduced the incidence of allograft rejection, these agents have also rendered patients highly susceptible to common and opportunistic infections.(1) Infections during the early period after SOT are often donor- or recipient-derived or are associated with surgical and nosocomial complications. Various opportunistic infections occur later, at 1–6 months after SOT, when the impact of potent immunosuppression is most intense. Risk of infection generally

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diminishes 6 months after SOT, because immunosuppressive agents are tapered to minimal levels in SOT recipients with satisfactory allograft function.(1)

Liver transplantation is a technically complex procedure that is performed in a potentially-contaminated environment within the abdominal cavity. Many liver transplant candidates are in an extremely morbid condition at the time of liver transplantation.(2) Intra-abdominal infections and peritonitis are the predominant sites of post-operative infections, and these generally occur during the first 2 months after liver transplantation.(2–4) In one study, over 50% of intra-abdominal infections and peritonitis were accompanied by bacteremia.(2) These infections are often associated with poor immediate and long-term outcomes. Courses of antibacterial therapy are therefore used commonly after liver transplantation, and their efficacy is dependent on the microbiology of such infections. Occasionally, the microbiology of bacteremia may not be defined particularly in patients who received empiric courses of antimicrobial therapy prior to obtaining specimens for bacterial cultures. We therefore aimed to assess the spectrum of bacteremia in relation to its onset after liver transplantation. In the process, we compared the clinical and microbiologic characteristics of patients who developed early-onset (defined as ≤ 2 months) and late-onset (> 2 months) bacteremia after liver transplantation.

PATIENTS AND METHODS

Study Population

The study population consisted of all consenting adult liver transplant recipients at the Mayo Clinic (Rochester, MN) during the period between January 1997 and March 2006. At initial clinic visit, all patients were requested to provide consent for the review of their medical records for research. As per Minnesota statute, only patients who provided this consent are included in this study. Of the 755 patients who underwent the first liver transplant during this period, eighteen patients did not provide informed consent for participation in research and were excluded. Hence, a total of 737 liver transplant recipients were included in this retrospective study. The study was approved by the Institutional Review Board of Mayo Foundation.

Standard Post-transplant Care

All liver transplant recipients received perioperative cefotaxime prophylaxis (1 gram intravenously every 8 hours) for 48 hours after transplantation. Penicillin and cephalosporin-allergic patients received intravenous vancomycin and ciprofloxacin. Oral selective bowel decontamination (consisting of gentamicin, nystatin, and colistin) was given to all patients during their hospitalization for liver transplantation. *Pneumocystis jirovecii* prophylaxis consisted of trimethoprim-sulfamethoxazole, at single-strength tablet once daily, for 4 months after liver transplantation. Antifungal prophylaxis with fluconazole (or amphotericin B preparation) was given to all high-risk patients, including those with fulminant hepatic failure, massive blood loss, re-transplantation, and major re-operations. Anti-cytomegalovirus (CMV) prophylaxis consisted of oral ganciclovir (prior to 2002; dose, 1 gram orally three times daily) or valganciclovir (since 2002; dose, 900-mg once daily) for 3 months to all CMV-donor positive/recipient-negative patients. Acyclovir prophylaxis (400 mg orally twice daily) was provided for 4 weeks to patients not receiving oral ganciclovir or valganciclovir. In the majority of patients, high-doses of steroids are given after liver transplantation. Thereafter, patients are maintained on tacrolimus (or cyclosporine), mycophenolate mofetil (or azathioprine), and prednisone during the early period after transplantation. The goal is to taper immunosuppression to tacrolimus monotherapy by 4 months, with mycophenolate mofetil and prednisone discontinued sequentially at 2–4 months after liver transplantation.

Classification of Bacteremia

All patients with Gram-positive bacteremia (GPB) and Gram-negative bacteremia (GNB) after liver transplantation were identified based on the review of the clinical and microbiology records. Only the first episode of GPB or GNB from each patient was included in the analysis. Patients with isolated single-bottle bacteremia due to common skin contaminants (such as coagulase-negative staphylococci, *Bacillus* species, *Corynebacterium* species, and *Propionibacterium* species) were excluded. The microbiology laboratory at the Mayo Clinic is certified by the College of American Pathologists and uses standard microbiology techniques according to the Clinical and Laboratory Standards Institute for identification of microorganisms in blood cultures and in vitro antimicrobial susceptibility testing.

Definitions of Clinical Data

The clinical and microbiological characteristics and outcomes of patients with episodes of early-onset and late-onset bacteremia were compared. Early-onset bacteremia was defined as bacteremia occurring within 2 months (60 days) after liver transplantation while those occurring beyond this period were classified as late-onset bacteremia. Nosocomial bacteremia was defined as a positive blood culture obtained from a patient who had been hospitalized for at least 48 hours. If a patient had been transferred from another hospital, the duration of inpatient stay was calculated from the date of the first hospital admission.(5) Initial sepsis grade within 48 hours of the day of the first positive blood culture was defined as described elsewhere.(6) Empiric antibiotic therapy was considered to be appropriate if the empirical therapy provided during the first 48 hours after the onset of bacteremia included at least one antibiotic to which the isolate was susceptible to and if the dose was adequate.(7) The primary source of bacteremia was defined using the Centers for Disease Control and Prevention criteria.(8) Outcomes of bacteremia were recurrence rate and mortality. Recurrence of bacteremia was defined as the isolation of the same species after documentation of negative blood cultures or clinical improvement after completing a course of appropriate antibiotic therapy. All-cause mortality was determined at 30-days and 90-days after the date of the first positive blood culture.

Statistical Analysis

All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL). Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were analyzed by the Student's *t* test. All tests were two-tailed and differences were considered significant at $P < 0.05$.

RESULTS

Characteristics of Patients with Bacteremia after Liver Transplantation

A total of 123 patients (16.7%; 95% confidence interval [95%CI] = 14.2%–19.6%) with either GPB or GNB were identified among 737 liver transplant recipients during the median follow-up period of 5.8 years (interquartile range [IQR] = 2.5–8.8 years). Ninety-two of the 737 patients (12.5%) had at least one episode of GPB, while 47 patients (6.4%) had at least one episode of GNB. Sixteen (2.2%) patients had experienced both GPB and GNB after liver transplantation. The patients were receiving prednisone (72.4%), tacrolimus (81.3%) or cyclosporine (10.6%), and mycophenolate mofetil (54.5%) or azathioprine (8.9%) as maintenance immunosuppressive drugs at the onset of bacteremia.

Table 1 shows the demographic and clinical characteristics of the 123 liver transplant recipients with bacteremia and 614 without bacteremia. Cytomegalovirus disease (20.3% vs. 10.9%, P=0.004) was significantly more common and there was trend for higher rate of re-

operation within 1 month (20.3% vs. 14.0%, *P*=0.07) and allograft rejection (49.6% vs. 41.4%, *P*=0.09) among patients with bacteremia compared to those without bacteremia.

Spectrum of Early- vs. Late-Onset Gram-Positive Bacteremia

Of the 92 patients with GPB, 54 (58.7%) were classified as having early-onset GPB. The majority (50 of 54 patients [92.6%]) of early-onset GPB occurred within 30 days and only four (7.4%) developed it 31–60 days after liver transplantation. The median interval from liver transplantation to the onset of early-onset GPB was 13 days (IQR = 8–21 days). *Staphylococcus* species (*S. aureus*, 35.2% [methicillin-resistance rate, 31.6%], coagulase-negative staphylococci, 18.5% [methicillin-resistance rate, 90%]) and *Enterococcus faecium* (16.7% [vancomycin resistance rate, 22.2%]) were the most common pathogens causing early-onset GPB. The remaining 38 patients (41.3%) were classified as having late-onset GPB. The median interval from liver transplant to the onset of late-onset GPB was 592 days (IQR = 137–1560 days). *Enterococcus faecalis* and *Streptococcus* species were the predominant pathogens causing late-onset GPB.

Comparing the clinical and microbiological characteristics of liver recipients with early- and late-onset GPB (table 2), the rate of nosocomial bacteremia was significantly higher in early- than late-onset GPB (66.7% vs. 23.7%, *P*<0.001). As primary sources of GPB, peritonitis (33.3% vs. 7.9%, *P*=0.004) and surgical wound infections (13.0% vs. 0%, *P*=0.04) were significantly more common in early- than late-onset GPB. Eighteen cases of early-onset GPB had underlying peritonitis, and all 18 infections were associated with post-operative complications, including seven with biliary leakage. The median interval from liver transplantation to peritonitis-associated GPB in these 18 patients was 14 days (IQR = 10–28 days). *Enterococcus* species was the predominant pathogen (11 of 18 patients [61.1%] with peritonitis) while *Staphylococcus aureus* was the infecting pathogen in only 4 patients (22.2%). On the other hand, all three patients with peritonitis-associated late-onset GPB (onset at 1122, 1556, and 2026 days after liver transplantation) had spontaneous bacterial peritonitis due to viridans streptococci or coagulase-negative staphylococci. In seven patients with early-onset GPB, this was associated with surgical wound infection; in these patients, the median interval from liver transplantation to GPB was 13 days (IQR = 10–17 days), and *S. aureus* was the cause of GPB in six of the seven cases (85.7%). Biliary infection (18.4% vs. 3.7%, *P*=0.03) and skin and soft tissue infection (13.2% vs. 0%, *P*=0.01) as sources of bacteremia were more commonly observed in the late-onset compared to early-onset GPB group. All five patients with GPB associated with skin and soft tissue infection had streptococcal cellulitis (*S. pyogenes*, *S. agalactiae*, and group C streptococci) or other soft tissue infections.

The proportion of catheter-related bacteremia (22.2% vs. 13.2%, *P*=0.27) did not significantly differ between early- and late-onset GPB. *Staphylococcus* species was more common in early- than late-onset catheter-related GPB (*S. aureus*, 5/12 [41.7%] vs. 1/5 [20.0%], *P*=0.60; coagulase-negative staphylococci, 5/12 [41.7%] vs. 1/5 [20.0%], *P*=0.60), although this did not reach statistical significance. In contrast, enterococci were more common in late- than early-onset catheter-related GPB (2/12 [16.7%] vs. 3/5 [60.0%], *P*=0.12); however, these differences were not significant statistically.

Assessing the microbiology of GPB, *S. aureus* (35.2% vs. 5.3%, *P*=0.001) and *Enterococcus faecium* (16.7% vs. 2.6%, *P*=0.04) were significantly more common in patients with early- than late-onset GPB, respectively. In contrast, *Enterococcus faecalis* (22.2% vs. 47.4%, *P*=0.01) and *Streptococcus* species (9.3% vs. 34.2%, *P*=0.003) were more common in late-onset compared to early-onset GPB. The all-cause mortality did not differ significantly between early- and late-onset GPB.

Spectrum of Early- vs. Late-Onset Gram-Negative Bacteremia

Of the 47 patients with GNB, only 17 (36.2%) cases occurred early (early-onset GNB). Ten of the 17 patients (58.8%) developed GNB within 30 days after liver transplantation while seven (41.2%) developed it between 31–60 days. The median interval from liver transplantation to the onset of early-onset GNB was 20 days (IQR = 10–48 days). The most common pathogens causing early-onset GNB were anaerobic Gram-negative bacilli, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*; some were polymicrobial GNB. On the other hand, thirty patients (63.8%) developed late-onset GNB, with a median onset of 609 days (IQR = 215–1335 days) after liver transplantation. The most common pathogen causing late-onset GNB was *Escherichia coli*.

Comparing the clinical and microbiological characteristics of patients with early- and late-onset GNB (table 3), we found a significantly higher proportion of patients with early-onset GNB to have nosocomial bacteremia (70.6% vs. 20.0%, P=0.001). As primary source of GNB, peritonitis was more common in patients with early-onset than with late-onset GNB (41.2% vs. 6.7%, P=0.007). All seven patients with peritonitis and early-onset GNB had post-operative surgical complications including biliary leakage in three patients; the median interval from liver transplantation to GNB was 19 days (IQR = 10–52 days). Anaerobic Gram-negative bacteria were the cause of GNB in four of these seven patients (three with *Bacteroides fragilis* and one with *Prevotella buccae*), while *P. aeruginosa* was isolated in two patients (28.6%). In contrast, only two patients with late-onset GNB had peritonitis; in one case, it was post-operative peritonitis caused by *Bacteroides distasonis* and *E. faecium* and in the second case, it was associated with spontaneous bacterial peritonitis caused by *Enterobacter sakazaki*.

Assessing the microbiology of GNB, *P. aeruginosa* (29.4% vs. 3.3%, P=0.02) and Gram-negative anaerobes (41.2% vs. 6.7%, P=0.007) were more common in early- than late-onset GNB. In contrast, *E. coli* (0% vs. 46.7%, P=0.001) was more common in late-onset compared to early-onset GNB. However, all other variables along with the all-cause mortality did not differ significantly between the early-onset and late-onset GNB groups.

Clinical Differences between Gram-Positive vs. Gram-Negative Bacteremia

Table 4 shows the clinical characteristics and outcomes of patients with GPB and GNB. GPB was significantly more common than was GNB during the early period (≤ 2 months) after liver transplantation (58.7% vs. 36.2%, P=0.01). Severe sepsis or septic shock (38.3% vs. 19.5%, P=0.02) was significantly more common with GNB compared to GPB. Notably, initial treatment with inappropriate empiric antibiotics (31.9% vs. 14.1%, P=0.01) was significantly more frequent in patients with GNB compared to GPB. In terms of the primary sources of bacteremia, urinary tract infection (4.3% vs. 19.1%, P=0.01) was more common with GNB while central venous catheter-related bacteremia (18.5% vs. 4.3%, P=0.02) was more common with GPB. Recurrence of bacteremia and all-cause mortality rates did not differ significantly between GPB and GNB.

Microbiology and Microbial Resistance Rates over Time

To determine microbial trends over the study period, we compared the microbiology and antimicrobial resistance rates during the first and second halves of the study (table 5). There was non-statistically significant higher rate of *Staphylococcus* species (32.2% vs. 18.8%, P=0.07) during the first 5 years of the study; however, the proportions of *S. aureus* and coagulase-negative staphylococci were not significantly different between two periods. In contrast, there was non-statistically significant higher rate of *Enterococcus* species (22.0% vs. 36.3%, P=0.07) during the second 5 years, and the proportion of *E. faecalis* (11.9% vs. 28.8%, P=0.02) was significantly higher. The antimicrobial resistance rates were not

significantly different between two periods (table 5). There were no cases of extended-spectrum β-lactamase producing *E. coli* and *K. pneumoniae*.

DISCUSSION

This study, which investigated the clinical and microbiological characteristics of bacteremia in a large cohort of over 700 liver transplant recipients, demonstrated several findings with important implications in direct patient care. Bacteremia commonly occurs in liver transplant recipients, with the majority of cases occurring within the first 1–2 months after liver transplantation. Important risk and associated factors include peritonitis, surgical wound infections, biliary tract infections, and presence of indwelling catheters. In addition, abdominal reoperation, allograft rejection, and cytomegalovirus disease are potential risk factors for bacteremia after liver transplantation. The etiology of bacteremia varied depending on time to onset after liver transplantation, potential source and other clinical variables. These factors have immediate implications in patient care, since suspected bacteremias are initially treated empirically prior to the identification of the offending organism and knowledge of its antimicrobial susceptibility pattern. Choosing the appropriate initial empiric antimicrobial regimen is critical to reducing infection-related and overall mortality.

As demonstrated in this study, bacteremia remains as a common complication after liver transplantation. The incidence rate of 16.7% in this study is comparable to previous reports from other centers; previous studies found that 34 of 144 liver transplant recipients (23.6%, 95% CI = 17.4%–31.2%) in South Korea,(9) 50 of 233 (21.5%, 95% CI = 16.7%–27.2%) in the USA,(10) and 91 of 392 (23.2%, 95% CI = 19.3%–27.7%) in Spain,(11) experienced bacteremia after liver transplantation. Similar to these prior studies, the majority of bacteremias occur during the first 1–2 months after liver transplantation. Our findings are also in agreement with previous reports that GPB is much more frequent than is GNB,(9) especially during the early period.(11) It is possible that the cefotaxime that is used as perioperative prophylaxis may have prevented much more cases of Gram-negative infections, but may not have been optimal to prevent infections due to methicillin-resistant *Staphylococcus* species and enterococcus. In this regard, one may predict that the microbiological pattern of bacteremia and other infectious diseases may vary depending on the transplant center's protocol for antimicrobial prophylaxis.

In contrast to traditional timeline that bacterial infections occur most commonly during the first month, we defined early-onset bacteremia in this study as infection occurring within 2 months after liver transplantation. We observed that, in the current era, one month may be too short of a time period to capture all bacterial infections related to post-operative complications. Indeed, our data showed that while the majority of early-onset GPB (92.6%) and GNB (58.8%) occurred within 30 days, a large number (7.4% of early-onset GPB, and 41.2% of early-onset GNB) occurred 31–60 days after liver transplantation. The most frequently observed surgical site infections associated with bacteremia are intra-abdominal abscesses, peritonitis, and wound infections.(2, 3) A prospective study found that 56% of surgical site infections occurred within 2 weeks after liver transplantation, whereas 21% occurred after 5 weeks.(2) In another study, the average time to the onset of peritonitis was 37 days after liver transplantation while the average time to surgical wound infection 47 days.(3) Hence, many of the bacterial infections traditionally described occurring during the first month may still occur commonly during the second month, especially those with risk factors such as biliary leakage,(3) which occurs in 17.1% of living-donor and 6.8% of deceased-donor liver transplantation.(12)

Bacterial peritonitis as the primary source of bacteremia was more common with early-onset compared to late-onset GPB (33.3% vs. 7.9%, *P*=0.004) and GNB (41.2% vs. 6.7%, *P*=0.007). In all 25 patients with early bacteremic peritonitis, there was an association with post-operative complications, including biliary leakage in 10 patients. Previous studies found that post-operative peritonitis occurred 18–55 days after liver transplantation(13) and intra-abdominal infections were observed more commonly within 100 days after liver transplantation.(14) Had we defined early-onset bacteremia as infections occurring within 30 days after liver transplantation, peritonitis (50.0% vs. 10.8%, *P*=0.01) would have also been significantly more frequent in patients with early-onset than with late-onset GNB, and there was also a trend for higher peritonitis (30.0% vs. 14.3%, *P*=0.07) and wound infection (12.0% vs. 2.4%, *P*=0.12) in patients with early-onset compared to late-onset GPB.

In contrast, one of the major predisposing factors for late-onset bacteremia is biliary tract infection. These infections are often associated with biliary strictures, which has been described to occur in 15.2% of living-donor and 7.5% of deceased-donor liver transplant recipients.(12) Biliary infections related to biliary strictures occur at a much later time point compared to peritonitis and wound infections.(3, 13) Previous studies showed that the average time to onset of biliary infection was 80 days (3) and that cholangitis occurred 28–69 days after liver transplantation.(13) Accordingly, in our study, biliary infections were observed less frequently in early- compared to late-onset GPB (3.7% vs. 18.4%, *P*=0.03) and GNB (5.9% vs. 30.0%, *P*=0.07).

Because of the differences in the predisposing factors, there are important differences in the spectrum of bacteriology between early-onset and late-onset bacteremia. In our study, *S. aureus*, coagulase-negative staphylococci, *E faecium*, *P. aeruginosa*, and Gram-negative anaerobes are the predominant pathogens during the first 2 months. These pathogens should therefore be considered as potential causes of early-onset bacteremia in patients presenting with sepsis during the first 2 months after liver transplantation, and treated adequately. In contrast, *E. coli*, *E. faecalis*, and *Streptococcus* species predominate beyond the second month after liver transplantation. The clinical manifestations of severe sepsis or septic shock would further suggest that the bacteremia is more likely due to Gram-negative pathogens. The initial antimicrobial coverage of these infections should take into consideration the local antibiogram pattern, including knowledge of methicillin-resistance rates for staphylococcal species, vancomycin-resistance rates for enterococci, and extended beta-lactamase production among *E coli*, *Klebsiella* species and other Gram-negative bacteria. Other clinical variables such as the presence of indwelling vascular catheters (*Staphylococcus* species is most common pathogen, potentially with high methicillin-resistance rates), peritonitis (*Enterococcus* species, possibly with vancomycin resistance for colonized patients), surgical wound infections (*Staphylococcus* species is most common pathogen), urinary infections (Gram-negative bacteria), and biliary infections (often polymicrobial) would further aid in determining the potential etiology. Moreover, recent and current antimicrobial use (such as cefotaxime antibacterial prophylaxis [which does not prevent against methicillin-resistant *Staphylococcus* species, enterococci and *Pseudomonas* species] and oral selective bowel decontamination [which may not contain good anti-Gram positive coverage]) likely affects the microbiology of infections. Knowledge of these factors is therefore important during the critical period of initial empiric antibacterial therapy. Providing adequate empiric antibacterial coverage during this period, while waiting for bacterial identity and susceptibility pattern, is essential in ensuring a favorable outcome of bacteremia.

Abbreviations

CI	confidence interval
CNS	coagulase-negative staphylococci
GNB	Gram-negative bacteremia
GPB	Gram-positive bacteremia
IQR	interquartile range
SD	standard deviation
SOT	solid organ transplantation

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TABLE 1

Demographic and Clinical Characteristics of liver transplant patients with and without bacteremia

Characteristic	Patients with bacteremia (n = 123)	Patients without bacteremia (n = 614)	*P* Value
Demographics			
Age, mean years ± SD	52 ± 10	52 ± 11	0.76
Male	77 (62.6)	393 (64.0)	0.77
Caucasian	115 (93.5)	556 (90.6)	0.30
Donor			
Donor age, mean years ± SD	43 ± 16	42 ± 18	0.96
Deceased donor	107 (87.0)	568 (92.5)	0.04
Transplantation year			
1997–2001	68 (55.3)	316 (51.5)	0.44
2002–2006	55 (44.7)	298 (48.5)	
Liver Disease			
Hepatitis C	30 (24.4)	144 (23.5)	0.82
Hepatitis B	4 (3.3)	43 (7.0)	0.12
Alcoholic liver disease	22 (17.9)	133 (21.7)	0.35
Primary sclerosing cholangitis	27 (22.0)	104 (16.9)	0.18
Primary biliary cirrhosis	8 (6.5)	52 (8.5)	0.47
Autoimmune hepatitis	5 (4.1)	20 (3.3)	0.59
Malignancy			
Hepatocellular carcinoma	18 (14.6)	115 (18.7)	0.28
Cholangiocellular carcinoma	14 (11.4)	49 (8.0)	0.22
Other comorbid diseases			
Diabetes mellitus	31 (25.2)	122 (19.9)	0.18
Hypertension	33 (26.8)	139 (22.6)	0.32
Chronic kidney disease	26 (21.1)	113 (18.4)	0.48
Dialysis requirement	5 (4.1)	18 (2.9)	0.57
Cardiomyopathy	4 (3.3)	38 (6.2)	0.20
Ulcerative colitis	13 (10.6)	48 (7.8)	0.31
Post-transplant events			
Re-operation within 1 month	25 (20.3)	86 (14.0)	0.07
Cytomegalovirus disease	25 (20.3)	67 (10.9)	0.004
Allograft rejection	61 (49.6)	254 (41.4)	0.09

NOTE: Data are numbers (%) of patients, unless otherwise indicated. SD, standard deviation.

TABLE 2

Comparison of Clinical Characteristics of Liver Transplant Patients with Early- and Late-onset Gram-Positive Bacteremia

	Early GPB (*n* = 54)	Late GPB (*n* = 38)	*P* Value
Nosocomial bacteremia	36 (66.7)	9 (23.7)	<0.001
Initial sepsis grade			
Sepsis	46 (85.2)	28 (73.7)	0.17
Severe sepsis	6 (11.1)	8 (21.1)	0.19
Septic shock	2 (3.7)	2 (5.3)	1.00
Inappropriate empirical antibiotics	10 (18.5)	3 (7.9)	0.15
Bacterial resistance to antibiotics	6 (11.1)	2 (5.3)	0.46
Inadequate dose of antibiotics	4 (7.4)	1 (2.6)	0.40
Primary source			
Biliary	2 (3.7)	7 (18.4)	0.03
Peritonitis	18 (33.3)	3 (7.9)	0.004
Urinary tract	1 (1.9)	3 (7.9)	0.30
Liver abscess	1 (1.9)	5 (13.2)	0.08
Catheter-related	12 (22.2)	5 (13.2)	0.27
Pneumonia	0 (0)	1 (2.6)	0.41
Skin and soft tissue	0 (0)	5 (13.2)	0.01
Wound	7 (13.0)	0 (0)	0.04
Unknown	9 (16.7)	4 (10.5)	0.41
Others	4 (7.4)	5 (13.2)	0.48
Microorganisms			
Staphylococcus spp.	29 (53.7)	5 (13.2)	<0.001
Staphylococcus aureus	19 (35.2)	2 (5.3)	0.001
Coagulase-negative staphyloccus	10 (18.5)	3 (7.9)	0.15
Enterococcus spp.	22 (40.7)	20 (52.6)	0.26
Enterococcus faecium	9 (16.7)	1 (2.6)	0.04
Enterococcus faecalis	12 (22.2)	18 (47.4)	0.01
Streptococcus spp.	5 (9.3)	13 (34.2)	0.003
Anaerobes	1 (1.9)	3 (7.9)	0.30
Polymicrobial bacteremia	7 (13.0)	6 (15.8)	0.70
Antibiotic resistance			
Methicillin resistance/no. of *S. aureus*	6/19 (31.6)	2/2 (100)	0.13
Methicillin resistance/no. of CNS	9/10 (90.0)	2/3 (66.7)	0.42
Vancomycin resistance/no. of *E. faecium*	2/9 (22.2)	1/1 (100)	0.30
Vancomycin resistance/no. of *E. faecalis*	0/12 (0)	0/18 (0)	-
Recurrence of bacteremia	7 (13.0)	2 (5.3)	0.30
30-day all-cause mortality	5 (9.3)	4 (10.5)	1.00
90-day all-cause mortality	7 (13.0)	7 (18.4)	0.47

NOTE: Data are numbers (%) of patients. CNS, coagulase-negative staphylococci; GPB, Gram-positive bacteremia.

TABLE 3

Comparison of Clinical Characteristics of Liver Transplant Patients with Early- and Late-onset Gram-Negative Bacteremia

	Early GNB (*n* = 17)	Late GNB (*n* = 30)	*P*
Nosocomial bacteremia	12 (70.6)	6 (20.0)	0.001
Initial sepsis grade			
Sepsis	12 (70.6)	17 (56.7)	0.35
Severe sepsis	4 (23.5)	8 (26.7)	1.00
Septic shock	1 (5.9)	5 (16.7)	0.40
Inappropriate empirical antibiotics	8 (47.1)	7 (23.3)	0.09
Bacterial resistance to antibiotics	7 (41.2)	4 (13.3)	0.07
Inadequate dose of antibiotics	1 (5.9)	3 (10.0)	1.00
Primary source			
Biliary	1 (5.9)	9 (30.0)	0.07
Peritonitis	7 (41.2)	2 (6.7)	0.007
Urinary tract	2 (11.8)	7 (23.3)	0.46
Liver abscess	2 (11.8)	0 (0)	0.13
Catheter-related	1 (5.9)	1 (3.3)	1.00
Pneumonia	1 (5.9)	1 (3.3)	1.00
Skin and soft tissue	0 (0)	1 (3.3)	0.45
Wound	0 (0)	0 (0)	-
Unknown	1 (5.9)	4 (13.3)	0.64
Others	2 (11.8)	6 (20.0)	0.69
Microorganisms			
Enterobacteriaceae	5 (29.4)	26 (86.7)	<0.001
Escherichia coli	0 (0)	14 (46.7)	0.001
Klebsiella pneumoniae	3 (17.6)	6 (20.0)	0.84
Enterobacter spp.	1 (5.9)	5 (16.7)	0.40
Non-fermentatives	6 (35.3)	3 (10.0)	0.05
Pseudomonas aeruginosa	5 (29.4)	1 (3.3)	0.02
Anaerobes	7 (41.2)	2 (6.7)	0.007
Polymicrobial bacteremia	3 (17.6)	5 (16.7)	1.00
Antibiotic resistance			
Enterobacteriaceae			
Cefotaxime-resistance	0/5 (0)	1/26 (3.8)	1.00
Ciprofloxacin-resistance	0/5 (0)	1/26 (3.8)	1.00
Non-fermentatives			
Ciprofloxacin-resistance	1/6 (16.7)	0/3 (0)	1.00
Imipenem-resistance	3/6 (50.0)	0/3 (0)	0.46
Recurrence of bacteremia	2 (11.8)	1 (3.3)	0.54
30-day all-cause mortality	1 (5.9)	4 (13.3)	0.64
90-day all-cause mortality	2 (11.8)	5 (16.7)	1.00

NOTE: Data are numbers (%) of patients. GNB, Gram-negative bacteremia. There are no cases of infection due to extended β-lactamase producing bacteria.

TABLE 4

Comparison of Clinical Characteristics of Liver Transplant Patients with Gram-Positive and Gram-Negative Bacteremia

	GPB (*n* = 92)	GNB (*n* = 47)	*P*
Early and late bacteremia			
Early	54 (58.7)	17 (36.2)	0.01
Late	38 (41.3)	30 (63.8)	
Nosocomial bacteremia	45 (48.9)	18 (38.3)	0.23
Initial sepsis grade			
Sepsis	74 (80.4)	29 (61.7)	0.02
Severe sepsis	14 (15.2)	12 (25.5)	0.14
Septic shock	4 (4.3)	6 (12.8)	0.09
Inappropriate empirical antibiotics	13 (14.1)	15 (31.9)	0.01
Primary source			
Biliary	9 (9.8)	10 (21.3)	0.06
Peritonitis	21 (22.8)	9 (19.1)	0.62
Urinary tract	4 (4.3)	9 (19.1)	0.01
Liver abscess	6 (6.5)	2 (4.3)	0.72
Catheter-related	17 (18.5)	2 (4.3)	0.02
Pneumonia	1 (1.1)	2 (4.3)	0.26
Skin and soft tissue	5 (5.4)	1 (2.1)	0.66
Wound	7 (7.6)	0 (0)	0.10
Unknown	13 (14.1)	5 (10.6)	0.56
Others	9 (9.8)	7 (14.9)	0.37
Polymicrobial bacteremia	13 (14.1)	8 (17.0)	0.65
Recurrence of bacteremia	9 (9.8)	3 (6.4)	0.75
30-day all-cause mortality	9 (9.8)	5 (10.6)	1.00
90-day all-cause mortality	14 (15.2)	7 (14.9)	0.96

NOTE: Data are numbers (%) of patients. GNB, Gram-negative bacteremia; GPB, Gram-positive bacteremia.

TABLE 5

Microbiology and Antimicrobial Resistance Patterns over Time

	1997–2001 (*n* = 59)	2002–2006 (*n* = 80)	*P* Value
Microorganisms			
Staphylococcus spp.	19 (32.2)	15 (18.8)	0.07
Staphylococcus aureus	12 (20.3)	9 (11.3)	0.14
Coagulase-negative staphylococcus	7 (11.9)	6 (7.5)	0.38
Enterococcus spp.	13 (22.0)	29 (36.3)	0.07
Enterococcus faecium	4 (6.8)	6 (7.5)	1.00
Enterococcus faecalis	7 (11.9)	23 (28.8)	0.02
Streptococcus spp.	7 (11.9)	11 (13.8)	0.74
Gram-positive anaerobes	0 (0)	4 (5.0)	0.14
Enterobacteriaceae	13 (22.0)	18 (22.5)	0.95
Escherichia coli	7 (11.9)	7 (8.8)	0.55
Klebsiella pneumoniae	3 (5.1)	6 (7.5)	0.73
Enterobacter spp.	3 (5.1)	3 (3.8)	0.70
Non-fermentatives	5 (8.5)	4 (5.0)	0.49
Pseudomonas aeruginosa	4 (6.8)	2 (2.5)	0.40
Gram-negative anaerobes	2 (3.4)	7 (8.8)	0.30
Antibiotic resistance			
Methicillin resistance/no. of *S. aureus*	5/12 (41.7)	3/9 (33.3)	1.00
Methicillin resistance/no. of CNS	6/7 (85.7)	5/6 (83.3)	1.00
Vancomycin resistance/no. of *E. faecium*	1/4 (25.0)	2/6 (33.3)	1.00
Vancomycin resistance/no. of *E. faecalis*	0/7 (0)	0/23 (0)	-
Enterobacteriaceae			
Cefotaxime-resistance	1/13 (7.7)	0/18 (0)	0.42
Ciprofloxacin-resistance	0/13 (0)	1/18 (5.6)	1.00
Non-fermentatives			
Ciprofloxacin-resistance	1/5 (20.0)	0/4 (0)	1.00
Imipenem-resistance	2/5 (40.0)	1/4 (25.0)	1.00

NOTE: Data are numbers (%) of patients. CNS, coagulase-negative staphylococci.