Perioperative Bacterial Infections in Deceased Donor and Living Donor Liver Transplant Recipients

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Background: **Deceased donor (DDLT) and living donor (LDLT) liver transplant (LT) is in vogue in several centers in India. Most centers are resorting to LDLT as a preferred surgery due to shortage of deceased donor liver. The risk of infection and its effect on survival in both groups of recipients from the Indian subcontinent are not known. The study was conducted to compare the bacterial infection rates among LDLT and DDLT recipients and their impact on survival at a tertiary referral center.** ***Methods:*** **Retrospective data on 67 LT recipients were reviewed. Data on pre-, per-, and postoperative bacterial infection rates and the common isolates were obtained.** ***Results:*** **Thirty-five patients had LDLT and 32 had DDLT. The prevalence of pre-operative bacterial infection and the isolates was similar in both groups. The perioperative bacterial infection rates were significantly higher in DDLT recipients ($P<0.01$) (relative risk: 1.44 95% confidence interval 1.04–1.9). In both LDLT and DDLT, the common source was urinary tract followed by bloodstream infection. The common bacterial isolates in either transplant were Klebsiella followed by *Escherichia coli*, Pseudomonas spp. and nonfermenting gram-negative bacteria. Six patients (four LDLT; two DDLT) were treated for tuberculosis. Among the risk factors, cold ischemic time, and duration of stay in the intensive care unit was significantly higher for DDLT ($P<0.01$). The death rates were not significantly different in the two groups. However, the odds for death were significantly high at 26.8 ($P<0.05$) for postoperative bacterial infection and 1.8 ($P<0.001$) for past alcohol.** ***Conclusion:*** **Liver transplant recipients are at high-risk for bacterial infection irrespective of type of transplant, more so in DDLT.** **(J Clin Exp Hepatol 2012;2:35–41)**

A major concern in the developing countries has been the higher rates of bacterial infection following renal[1] and bone marrow transplants.[2] Bacterial and fungal infection are the major cause of morbidity and mortality in liver transplant (LT) recipients. Risk for infection in a LT recipient is determined by a patient's 'net state of immunosuppression',[3] a balance contributed to by factors such as the dose, type, and duration of immunosuppressive therapy, the presence of indwelling devices such as catheters, nutritional status, metabolic status, viral infections, graft function, and underlying disease. Other risk factors for latent or an unrecognized infection in the donor or recipient include influence of multiple abdominal surgeries,[4–6] prolonged operative time (>12 hr), and reoperation.[7]

World over, in the past decade, survival rates after LT have steadily improved, with 1-year survival exceeding 85%. Majority of the reports are from centers in the West performing LT for over a decade. The improved survival has been attributed to the use of appropriate dosing and choice of immunosuppressants, improvement in diagnostic methods for identifying and preventing infections, and better surgical techniques.[8]

The aim of the study was to compare the bacterial infection rates among deceased donor LT (DDLT) and living donor LT (LDLT) recipients and their impact on survival at a tertiary referral center in the perioperative period, that is, pre-, per-, and postoperative period (until discharge/death following admission for LT).

METHODS

Data were collected retrospectively from the hospital records of 67 consecutive LT recipients operated between August 2009 and June 2011. Pre-operative information included age, sex, occupation, comorbid illness, information on pre-transplant dialysis, abdominal surgery, and invasive

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Abbreviations: AFB: acid fast bacilli; ATT: anti-tuberculous treatment; BAL: bronchoalveolar lavage; BSI: bloodstream infections; CIT: cold ischemic time; CLSI: Clinical and Laboratory Standards Institute; CRP: C-reactive protein; DDLT: deceased donor liver transplant; *E. coli*: *Escherichia coli*; ET: endotracheal; ICU: intensive care unit; *K. pneumonia*: *Klebsiella pneumonia*; LDLT: living donor liver transplant; LT: liver transplant; MELD: model for end-stage liver disease; MRSA: methicillin-resistant *Staphylococcus aureus*; NFGNB: nonfermenting gram-negative bacilli; *P. aeruginosa*: *Pseudomonas aeruginosa*; RFA: radiofrequency ablation; RR: relative risk; TACE: transarterial chemoembolization; TB: tuberculosis
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procedures like radiofrequency ablation (RFA) and transarterial chemoembolization (TACE).

As per the department protocol, culture specimens were obtained in the immediate pre-, per-, and postoperative period, i.e. until discharge/death, when there was a clinical suspicion of infection in the recipient. Postoperatively, cultures were done in the presence of symptoms or evidence of septicemia (fever, hemodynamic instability, leukocytosis, raised procalcitonin, and raised C-reactive protein [CRP]), respiratory infection, and infection at surgical wound site or drain fluid. Specimens for culture included blood, urine, sputum, bronchoalveolar lavage (BAL), endotracheal (ET) tube aspirate, drain fluid, and from surgical wound site. The date of onset, the probable source of infection, and organism isolate at these times were noted.

Following criteria were used to define infection, contamination, and colonizers: For blood samples, Clinical and Laboratory Standards Institute (CLSI) criteria were used to define contaminant,[9] colonizer, bacteremia, and infection. For urine samples, instead of the routine 100,000 CFU/mL, a count of 10,000/mL was considered significant along with the presence of leukocytes in urine (lower counts because of immunosuppressed state). Lactobacillus species, alfa-streptococci, and diphtheroids were considered as contaminants. Also, cultures containing three or more organisms were also considered as contaminants.

Staphylococcus aureus, Klebsiella spp. from surgical wound swabs, nonfermenting gram-negative bacilli (NFGNB) in the urine or catheter tip, Acinetobacter from sputum, ascitic fluid, and wound swabs were considered as colonizers. Contaminants included *Staphylococcus epidermidis* isolates from the skin, ascitic fluid, wound swabs, or catheter tips. Multiple isolates in any given culture sample were considered as contaminants and were also excluded. Also, isolated culture positive from wound swabs was not considered for analysis and was managed with local antibiotics and sterile dressings.

Following risk factors which could influence bacterial infection rates were noted. These included pre-operative levels of serum albumin (as a marker for nutritional status) and model for end-stage liver disease (MELD) scores (marker of severity of liver disease), LT performed as an emergency, that is, within 72 hours of admission, or as an elective procedure, total duration of hospital stay including number of days in intensive care unit (ICU), duration of intubation, cold ischemia time (CIT), duration of surgery, operative complications such as intra-abdominal bleeding, bowel perforation, hepatic artery thrombosis, the need for re-laparotomy, and finally drug details such as duration of steroid, the need for pulsing with high-dose steroids for acute rejection, and the need for basiliximab.

All patients were on piperacillin tazobactam for a period of 5 days as prophylaxis for infection. Standard protocol for immunosuppressant included the use of tacrolimus, mycophenolate mofetil, and steroid in standard dose, with dose adjustments for cellular rejection. Flucanozole was given in a dose of 200 mg/day for 3 months. Basiliximab was administered in the presence of renal dysfunction. Antivirals were administered whenever appropriate. Re-transplantation individuals were excluded.

Ethics Committee of the Institution approved the study.

Statistical Analysis

SPSS Version 16 software package. Tests of χ^2, ANOVA, relative risk (RR), and odds ratio for death through logistic regression were computed. The comparisons were set between DDLT and LDLT unless otherwise specified.

RESULTS

There were 32 patients who had DDLT and 35 had LDLT (Table 1). There were 2 patients who had swap liver and 3 had combined liver and kidney transplantation (one LDLT recipient received liver and kidney from 2 donors). Age and sex in either group were comparable. There were 15 children below the age of 14 years (youngest 5-month-old). Twelve children had LDLT and 2 DDLT. The median age in LDLT was 50 years (range 5 months to 68 years) vs 39.5 years (range 9–67 years) in DDLT. For DDLT, the male female ratio was 3:2 and was skewed toward males in LDLT (5.4:1). The number of patients who had a pre-transplant abdominal surgery was similar in both groups. Two patients each in both groups required pre-transplant renal dialysis. Among the 3 patients with hepatocellular carcinoma (HCC), 2 had RFA, and 1 had TACE.

Perioperative (Pre-, Per-, and Postoperative Period) Infection Rates

Three of 32 (9.3%) in DDLT and 13 of 35 (37.1%) patients in LDLT had no infection at any point of time. This was

Table 1 Baseline characteristics in deceased donor liver transplant and living donor liver transplant patients.

Characteristics	DDLT (32) Number (%)	LDLT (35) Number (%)
Sex (M:F)	27:5	21:14
Age (median in yr)	39.5 (6 mo to 67 yr)	50 (9 mo to 68 yr)
Children (<15 yr)	2 (6.25)	12 (34.2)
Comorbid illness		
DM	11 (34.3)	8 (22.8)
Hypertension	6 (18.8)	4 (11.4)
Hypothyroidism	6 (18.8)	1 (2.9)
History of TB	2 (6.3)	1 (2.9)
Pre-operative dialysis	2 (6.3)	2 (5.7)
Major abdominal surgery	8 (25)	9 (25.7)

DDLT: deceased donor liver transplant; DM: diabetes mellitus; LDLT: living donor liver transplant; TB: tuberculosis.

statistically significant ($P<0.01$). The RR for infection in DDLT was 1.44 (95% confidence interval [CI] 1.04–1.9).

Pre-operative Infection Rates

The overall prevalence of pre-operative bacterial infection in one or more culture samples was similar at 53.1% (17 patients) in DDLT vs 51.4% (18 patients) in LDLT (Table 2). The number of admissions for control of infection was similar in both groups; also, there were no differences in the organism isolated in both the groups. Single isolates were uncommon. Two DDLT recipients continued to be infected with same isolates at the time of surgery and in the postoperative period.

Per- and Postoperative Infection Rates

On the day of surgery, there were significantly more infections in DDLT recipients (10 recipients; 31.3%) compared with LDLT (3 recipients; 8.6%) ($P<0.05$). A similar pattern of significant difference was observed in the postoperative period between DDLT (24 recipients; 75%) and LDLT (15 recipients; 42.9%) recipients ($P<0.01$). The RR of infection in DDLT was 1.66 times compared with LDLT (95% CI 1.13–2.43).

BACTERIAL ISOLATES

Deceased Donor Liver Transplant

Tables 3 and 4 summarize the bacterial isolates in patients following DDLT. The most common single source of infection was urine (6/24) and blood (4/24). Unlike in LDLT, patients with bloodstream infections (BSI) in DDLT recipients had concurrent infection in ascitic fluid, respiratory tract, and urinary tract. One patient had methicillin-resistant *S. aureus* (MRSA) isolate both from blood and from catheter tip and one other patient had Acinetobacter isolated from blood alone. Klebsiella spp. was the common isolate from ascitic fluid, urine, and sputum (Table 4). *Escherichia coli* was also the common isolate in the urine. Pseudomonas was isolated from blood, urine, and the respiratory tract. *Burkholderia psuedomellei* was isolated in blood culture in one patient and *Serratia marcenses* from sputum in another patient.

Living Donor Liver Transplant

The most common site of postoperative infection was the urinary tract and was a single source of infection in 4 of the 15 patients and in combination with BSI in another 4 patients and with respiratory tract infection in 2 (Tables 3 and 5). Klebsiella spp. was the frequent isolate followed by *E. coli* and Enterococcus. Klebsiella spp. was also isolated from other sites (Table 5). *Acinetobacter baumannii* as a pathogen was isolated from ascitic fluid and respiratory tract. Isolated BSI was rare as also simultaneous infections in more than one site.

Six patients (4 LDLT; 2 DDLT) were treated for tuberculosis (TB), 3 as prophylaxis. Acid fast bacilli (AFB) were isolated from pleural fluid, skin lesions, cerebrospinal fluid, and liver in 3 patients.

Table 2 Pre-operative infection rates.

	DDLT (32) Number (%)	LDLT (35) Number (%)	*P* value
Pre-operative infection	17 (53.1)	18 (51.4)	NS
Average number of admissions	3.2	2.9	NS
Culture isolates			
Escherichia coli	2 (6.3)	7 (20)	NS
Klebsiella spp.	2 (6.3)	4 (11.4)	NS
Pseudomonas aeruginosa	1 (3.1)	2 (5.7)	NS

DDLT: deceased donor liver transplant; LDLT: living donor liver transplant; NS: nonsignificant; *P. aeruginosa*: *Pseudomonas aeruginosa*.

Table 3 Site of bacterial isolation in living donor liver transplant and deceased donor liver transplant from single/concurrent sources.

Source	DDLT (32) Number (%)	LDLT (35) Number (%)	*P* value
Blood	9 (28.1)	7 (20)	NS
Urine	10 (31.2)	10 (28.5)	NS
Drain	5 (15.6)	2 (5.7)	NS
Respiratory	3 (9.3)	3 (8.5)	NS
Catheter tip	3 (9.3)	1 (2.8)	NS

DDLT: deceased donor liver transplant; LDLT: living donor liver transplant; NS: nonsignificant.

Table 4 Postoperative bacterial isolates from various sites in 24 of 32 deceased donor liver transplant patients.

Site	MRSA	*Acinetobacter baumannii*	Klebsiella spp.	*Escherichia coli*	*Pseudomonas aeruginosa*	NFGNB	Enterococcus spp.
Blood	1	1	2	1	2	2	2
Urine	None	None	4	4	2	None	1
Ascitic fluid	None	None	6	2	1	None	1
Sputum	None	None	4	1	1	None	1
Tracheal aspirate/BAL	None	None	2	1	2	1	None
Catheter tip	1	None	3	1	None	1	None

BAL: broncheolar alveolar lavage; MRSA: methicillin resistant *Staphylococcus aureus*; NFGNB: nonfermenting gram-negative bacilli.

Table 5 Postoperative bacterial isolates from various sites in 15 of 35 living donor liver transplant patients.

Site	MRSA	*Acinetobacter baumannii*	Klebsiella spp.	*Escherichia coli*	*Pseudomonas aeruginosa*	NFGNB	Enterococcus spp.
Blood	None	None	2	1	None	1	1
Urine	None	None	5	2	1	None	2
Ascitic fluid	None	None	2	None	None	None	1
Sputum	None	None	1	3	1	None	None
Tracheal aspirate/BAL	None	2	2	None	None	1	None
Catheter tip	None	None	2	None	None	None	None

BAL: broncheolar alveolar lavage; MRSA: methicillin resistant *Staphylococcus aureus*; NFGNB: nonfermenting gram-negative bacilli.

Table 6 Pre- and postoperative risk factors predicting bacterial infection.

	DDLT (32)	LDLT (35)	*P* value
Pre-operative factors			
Mean albumin (g/dL)	2.6±0.63	2.12±0.52	<0.05
Mean MELD	20±7.9	21.3±8.4	NS
Per-operative factors			
Cold ischemic time (hr)	6.1±2.7	2.3±0.4	<0.01
Infection present (hr)	4.98	3.89	<0.01
No infection (hr)	2.36	3.42	
Emergency surgery (%)	12 (37.5)	1 (2.8)	RR 4.52 (95% CI: 1.69–12.07)
Postoperative factors			
Mean duration of surgery (range)	10 hr 20 min (6–21 hr)	10 hr 30 min (3–17 hr 30 min)	NS
Duration of intubation (median)	30 cases <1 day	28 cases <1 day	NS
Mean intensive care unit stay (days)	6.9±6.4	5±2.8	<0.05
Median hospital stay (range)	20 days (4–65 days)	22 days (4–70 days)	NS
Packed red blood cells transfused (median)	9 units	5 units	NS
Duration of drain tube in situ (days)	9	9	NS
Intra-abdominal bleeding (%)	4 (12.1)	2 (5.8)	NS
Bowel perforation	None	1	–
Hepatic artery thrombosis	1	None	–
Re-exploration	5	5	NS
Acute cellular rejection	4	3	NS
Pulse dose steroid	3	2	NS
Basiliximab	2	4	NS
Death within a week of transplant	3	1	NS
Sepsis-related death after a week of transplant	2	4	NS

CI: confidence interval; DDLT: deceased donor liver transplant; LDLT: living donor liver transplant; MELD: model for end-stage liver disease; NS: nonsignificant; RR: relative risk.

RISK FACTORS FOR BACTERIAL INFECTION

In the pre-operative period, mean albumin levels were slightly but significantly higher (2.6±0.63 mg/dL) in DDLT recipients compared with LDLT (2.12±0.52) (Table 6). Twelve of the 32 (37.5%) DDLT recipients were undertaken as an emergency, i.e. within 72 hours of registration compared with only 1 recipient in LDLT (RR: 4.5).

The overall mean CIT was significantly more in DDLT, i.e. 6.1±2.7 hours compared with LDLT at 2.3±0.4 hours (ANOVA $P<0.01$). In the subgroup analysis, the average CIT for DDLT was 4.98 hours in the presence of infection and 2.36 hours for those without infection. This difference was significant ($P<0.01$). For LDLT, the figures were 3.89 hours with infection and 3.42 hours without infection (not significant).

The incidence of bacterial infection in the postoperative period (Table 6) in the two groups was not influenced by duration of intubation or duration of surgery, retained drainage tube, postoperative surgery-related complications such as re-bleed, bowel perforation, re-laparotomy, use of basiliximab, rate of acute cellular rejection, and its management with pulse dose of steroids. However, the median number of units of packed red cells replaced was slightly higher in DDLT group. Also, the mean ICU stay was longer in DDLT group at 6.9±6.4 days compared with LDLT (5±2.8 days). Thus, among the risk factors CIT and duration of stay in the ICU were significantly higher for DDLT (ANOVA; $P<0.01$).

Death rates due to septicemia and multiple organ failure in both LDLT and DDLT were similar, though the overall death rates were slightly lower in LDLT, that is, 11.4% (4 patients) vs 18.8% (6 patients) in DDLT

(difference not significant). Three of 6 deaths in DDLT group and 1 of the 4 deaths in LDLT group occurred within a week of surgery due to septicemia. Three of the 10 deaths were patients who were air-lifted on a ventilator for DDLT. These patients had multiple bacterial isolates in culture, both at the time of surgery and in the immediate postoperative period.

A logistic regression for factors affecting death (age and sex of patient, previous history of alcohol intake, preoperative infection, type of surgery, postoperative infection rates, previous abdominal surgery, and previous renal dialysis) showed that the odds for death were significantly high at 26.8 ($P<0.05$) for postoperative bacterial infection and 1.8 ($P<0.001$) for past alcohol.

DISCUSSION

Infection in the early post-LT period (<1 month) is most commonly bacterial, although the risk of fungal infection is high. This is the period when patients are most immunosuppressed. In an autopsy series study of cases between 1982 and 1997, infection was the cause of death in 64% of 321 transplant patient.[10] The most common infection was bacterial (48%) followed by fungal (22%), and viral (12%). In another report, up to two-thirds of all LT patients had at least one episode of infection.[11] Other series have observed infection rates of 1–2.5 episodes per patient.[12–14]

In our series, bacterial infection was far more common among DDLT recipients, that is, 24 (75%) vs 15 (42.9%) for LDLT recipients. Majority of the infection occurred a week after LT, despite adequate antibiotic prophylaxis, more so for DDLT recipients.

Source of bacterial infection in any abdominal surgery in an immunocompetent host is often from indwelling stents, central vascular access sites, and external drainage catheters, or are related to foreign bodies, necrotic tissue, or prolonged endobronchial intubation.[3,15,16] In majority, BSI is often secondary to abdominal and respiratory infection.

The high rates of bacterial infection seem to be also true for LT recipients. In this study, pre- and postoperative infection rates were similar in both LDLT and DDLT, though postoperatively, there were numerically more infections among DDLT recipients. Urinary tract was the most common site for infection in both groups of patients followed by BSI. Isolated source was more common than concurrent infection.

The MRSA infection is a cause for concern in LT patients. In Hashimoto's series,[17–19] the most frequent pathogen isolated was MRSA. The authors concluded in three major studies that there was a need for surveillance culture periodically after LDLT to identify and prevent transmission of MRSA, even in the absence of pre-operative MRSA infection. In our series, MRSA infection was present in only one patient and was not a major concern for our LT patient. Recovery was uneventful in this patient.

Kim et al[20] studied the influence of pre-transplant bacterial and fungal infection on orthotopic LT in 223 recipients, 37 patients (16.6%) had a positive culture in one or more samples. The culture positive and culture negative groups differed significantly in end-stage liver disease score but showed no difference in Child–Pugh–Turcotte score, the presence of spontaneous bacterial peritonitis, hemodialysis, or duration of stay in the ICU or hospital. In our study, there were no pre-operative factors such as age, comorbid illness, pre-operative dialysis, and abdominal surgery which influenced the postoperative outcome. There was no difference in the MELD score as well. Serum albumin levels were significantly low in patients undergoing LDLT. This may not be a factor which truly represents the nutritional status in both the groups, since majority of them would be receiving albumin infusions periodically. The only significant postoperative factors in DDLT recipients which predicted a higher bacterial infection rate were cold ischemic time and duration of ICU stay. Also, the number of units of packed red cells infused was numerically more in this group.

Acinetobacter spp. is an important nosocomial pathogen and is responsible for a wide range of infections, including bacteremia, pneumonia, urinary tract infection, peritonitis, among others. Kim et al[21] in a study of 451 subjects who had undergone LDLT noted infectious complications due to Acinetobacter spp. appeared in 26 patients (5.8%) with a total of 37 episodes. The commonest presumed sources of infection were biliary tract (56.8%), lung (18.9%), intra-abdomen (16.2%), catheter (5.4%), and urinary tract in 1 patient (3.6%). In our series, *A. baumannii* was often isolated as a colonizer in sputum, drain fluid, catheter tip, and surgical wound. Lung was the source for Acinetobacter in 2 LDLT patients (both died) and in blood in 1 DDLT patient, who survived. Most of the bacterial infections were sensitive to carbapenum group of drugs, tigecycline, colistin, and polymyxin (Table 7). Hence, proper dose and duration of therapy made the mortality rate in both DDLT and LDLT without a statistical significance.

The LT recipients have an 18-fold increase in the prevalence of active TB infection and a 4-fold increase in the case fatality rate.[22] Although, it is optimal to treat latent TB prior to transplantation with close monitoring of liver function tests,[23–25] post-transplant hepatotoxicity due to isoniazid is always a management problem. Chan et al[26] from Hong Kong reported TB in 8 of 397 patients of LDLT (2%). The mean time of developing TB infection after LT was 9 months (range 4–20 months). In our series, there was no TB-related case fatality. In 1 patient, the explanted liver was positive for AFB, in 2 others diagnosis of TB was made a month after transplant. Histologically, the explanted liver showed areas of epithelioloid collections with central necrosis, occasional Langhans giant cells, and rim of lymphocytes suggestive of necrotizing granulomatous

Table 7 Sensitive antibiotics.

Organisms	Sensitive to antibiotics				
Klebsiella spp.	Colistin	Polymyxin	Imipenum	Meropenum	Tigecyclin
Escherichia coli	Colistin	Polymyxin	Imipenum	Meroneum	Tigecyclin
Acinetobacter baumanni	Colistin	Polymyxin	Imipenum	Vancomycin	Tigecyclin
Pseudomonas aeruginosa	Colistin	Polymyxin	Imipenum	Meropenum	Tigecyclin
Staphylococcus epidermidis	Teicoplanin	Vancomycin	Linezolid	Clindamycin	Tigecyclin
Enterococci spp.	Teicoplanin	Vancomycin	Linezolid	–	–

inflammation; Ziehl Neelsen stain was negative for AFB, but polymerase chain reaction was positive. This was on a background of multifocal moderately differentiated HCC in a cirrhotic liver.

This study has unfolded several important information on high bacterial infection rates in both DDLT and LDLT recipients in the Indian subcontinent. This high prevalence is akin to other transplant programs in India such as renal and bone marrow transplant. Jha et al[1] from a tertiary referral center in North India quote a bacterial infection rate of >50% in patients undergoing renal transplant with 20–40% succumbing to bacterial infection. In yet another study by George et al[2] from yet another tertiary center from South India on allogenic bone transplant, the bacterial infection rate was reported to be 34.9% with a death rate of 15%. What is responsible for such high rates of bacterial infection in various transplant programs is not clear. A collative data from other high volume centers undertaking LT programs in India could throw light on the true magnitude of bacterial infection in the Indian subcontinent and thereafter guidelines for prevention of these infections can be proposed.

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CONFLICTS OF INTEREST

All authors have none to declare.

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