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ORIGINAL ARTICLE

Infection in liver transplant recipients—Analysis of 68 cases at teaching hospital in Taiwan

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Background: In Taiwan, liver transplantation is a common treatment of end-stage liver diseases. Infection has a negative impact on the survival of these patients and their grafts. We evaluated the timing and frequency of infections, and the risk factors associated with infection and mortality in liver transplant recipients from Taiwan.
Methods: This retrospective study enrolled all adult patients who underwent orthotopic liver transplantation from January 2004 to November 2008 at a tertiary hospital in Taiwan.
Results: Sixty-eight patients were enrolled (male/female = 46/22) and average age was 51.3 years. Bacterial infection (26/68, 38.2%) was the most common infectious disease, with a rate of 0.3/1,000 person-days in the perioperative period, 0.27/1,000 person-days in the early operative period, and 0.38/1,000 person-days in the late-operative period. Operation-related complications increased the risk of bacterial infection. Biliary stricture was the most common operation-related complication, and this was associated with biliary tract infection ($p < 0.001$). The average time from first stent placement for biliary stricture by endoscopic retrograde cholangiography to biliary tract infection was 34.5 days. The overall mortality rate was 11.7%, and the mortality rate was 14% for patients with infections.
Conclusions: Bacterial infection was the most common type of infection in liver transplant recipients. Surgery-related complication, especially biliary tract stricture was risk factor for infection. We suggest that the current recommendations about the timing of endoscopic retrograde cholangiography intervention be reevaluated.

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Introduction

The first liver transplantation in Taiwan was performed in 1984. Since then, this procedure has been performed at many tertiary medical centers in Taiwan as treatment of patients with end-stage liver diseases. However, postoperative infection has a major negative impact on the survival of liver transplant recipients and their grafts. In the past few decades, researchers from numerous countries have described the incidence of infection, timing of infection onset, and risk factors for infections after liver transplantation.[1–9] However, such data are lacking for Taiwan. We conducted this study to determine the timing, frequency, and risk factors for infection in 68 liver transplant recipients at a teaching hospital in Taiwan.

Materials and methods

Patients and setting

China Medical University Hospital is a 2,000-bed teaching hospital in Taichung City, central Taiwan. This retrospective study included all adult patients ($n = 68$) who were at least 18 years of age and who received orthotopic liver transplantation (OLT) from January 2004 to November 2008. Medical charts were thoroughly reviewed and demographic data, clinical features, and outcomes were recorded and analyzed.

Diagnostic definitions

All diagnoses were based on the definitions proposed by Garbino et al.[10] An infectious episode was defined as the association of compatible clinical signs and symptoms, laboratory tests, and a microbial pathogen recovered from normally sterile body site, followed by the introduction of an antimicrobial regimen directed against the microorganism identified. Blood stream infection was defined by the presence of clinical signs of infection and the presence of microorganisms in at least one blood culture. Biliary tract infection (BTI) was defined by the typical clinical symptoms/signs and a positive culture from the drainage tube. Peritonitis was defined by the typical clinical symptoms/signs and the presence of positive peritoneal fluid cultures obtained by percutaneous drainage or during surgery. Soft tissue infection was defined by the isolation of a pathogen from the infected site, which was compatible with the signs of infection. Intra-abdominal abscess was defined by the presence of localized purulent fluid collection and positive microbiological culture. Pneumonia was defined by the typical clinical manifestations, laboratory data (including a positive culture), and a new infiltrate on chest radiography. Cytomegalovirus (CMV) infection was defined as the presence of: (1) seroconversion of CMV-specific IgG and IgM in a previously seronegative patient (primary infection); (2) four-fold or greater increase in the CMV IgG antibodies titer (secondary infection or reactivation) or positive serum CMV pp65 antigen; or (3) positive serum CMV polymerase chain reaction or culture. Fungal infection was diagnosed if patients had one of the following: (1) positive blood culture; (2) isolation of fungi from an abdominal specimen with evidence of peritonitis or intra-abdominal abscess; or (3) tissue invasion proved by biopsy. Herpes simplex virus (HSV) infection was diagnosed based on the typical oral or genital ulcer and positive virus culture. Herpes zoster was diagnosed based on the characteristic dermatome distribution of skin lesion.

Infection episodes that occurred after transplantation were classified as: perioperative (onset within 1 month), early operative (onset within 1—6 months), or late operative (onset after 6 months). The "successful deployment" of a stent [by endoscopic retrograde cholangiography (ERC)] or catheter [by percutaneous transhepatic cholangial drainage (PTCD)] was defined as the removal of a stent or catheter with no recurrence of clinical symptoms/signs of biliary tract obstruction based on cholangiography of the patent biliary tract. We defined a patient as "under treated" if the stent or catheter remained in place, but the biliary tract obstruction remained. Urgent transplantation was performed for fulminant hepatic failure.

Immunosuppressive therapy and diagnosis of transplant rejection

For immunosuppression, all transplant recipients received either cyclosporine- or tacrolimus-based combined regimens [cyclosporine/tacrolimus + mycophenolate mofetil/mycophynolate sodium + methylprednisolone (MTP)/prednisolone] after liver transplantation. A possibly acute rejection episode was diagnosed based on clinical findings and biochemical data. A liver biopsy was performed to confirm rejection. When there was clinical suspicion of acute rejection, MTP (1 g intravenously everyday) was given for 3 days, and was then replaced with oral prednisolone, which was tapered gradually.

Perioperative antimicrobial prophylaxis and surgical procedure

Cefotaxime (2 g, every 8 hours, intravenous drip) and ampicillin (1 g, every 6 hours, intravenous drip) were used as perioperative prophylactic antibiotics. If there were no signs or symptoms of infection, these agents were discontinued after 5 days. No prophylactic medication for *Pneumocystis jirovecii*, fungus or virus was given. Preemptive or targeted treatment strategy for CMV was adopted after liver transplant in our patients. All patients received choledochocholedochal anastomosis without T tube or stent placement.[11]

Statistical analysis

All results were analyzed using SPSS, Version 12.0 (SPSS Inc., Chicago, IL, USA). For categorical data, proportions were compared with the χ^2 test. Continuous variables were compared with an independent t test. The Kaplan-Meier method was used for survival analysis. A p value of 0.05 or less was considered statistically significant. We used univariate and multivariable logistic regression models to assess the independent association of various risk factors with occurrence of bacterial infection postliver transplantation event. For each potential risk factor, the odds

ratio for the occurrence of bacterial infection and the 95% confidence interval were estimated.

Results

Sixty-eight patients (72 transplants, 4 retransplants) were included in this study, 68% (46/68) were male, and the average age was 51.3 years. All patients were followed for more than 6 months, and 93% were followed for more than 1 year. Sixty-seven patients were CMV seropositive before OLT. The main reasons for first-time OLT were: chronic hepatitis C infection (29.4%), chronic hepatitis B infection (22.0%), and chronic hepatitis B infection with hepatocellular carcinoma (11.7%) (Table 1).

Postoperatively, 38% (26/68) of patients had bacterial infections (50 episodes), 12% (8/68) had viral infections (8 episodes), and 9% (6/68) had fungal infections (6 episodes). Among patients with bacterial infections, the onset of infection varied with time. There were 0.3/1,000 person-days in the perioperative phase, 0.27/1,000 person-days in the early operative phase, and 0.38/1,000 person-days in the late-operative phase (Fig. 1).

Table 2 summarizes the species of pathogens isolated during the postoperative period. For patients with bacterial infections ($n = 26$), *Escherichia coli* was the most common species (17 episodes, 34.0%), followed by *Pseudomonas aeruginosa* (13 episodes, 26.0%), and *Staphylococcus aureus* (4 episodes, 8.0%). For patients with viral infections ($n = 8$), four patients had HSV-1 infections as oral or labial lesions, three patients had varicella-zoster virus infection, and one patient had active CMV infection (which appeared 15 months after liver transplantation). For patients with invasive fungal infections ($n = 6$), two had candidemia (onset at 21 and 765 days after OLT), two had invasive pulmonary and cutaneous aspergillosis (onset at 14 and 110 days after OLT), and two had disseminated cryptococcosis (onset at 200 and 661 days after OLT). *Mycobacterium tuberculosis* (TB) infection occurred in one patient at 2 years after liver transplantation.

Table 1 Reasons for orthotopic liver transplantation

	Number	Percentage
Chronic liver disease		
HBV	15	22.0
HCV	20	29.4
HBV + HCV	2	2.94
HBV + HCC	8	11.7
HCV + HCC	4	5.88
HBV + HCV + HCC	1	1.47
Alcoholic liver cirrhosis	6	8.82
Primary biliary cirrhosis	1	1.47
Wilson's disease	1	1.47
Acute liver failure		
HBV-related	6	8.82
Others	4	5.88
Total	68	100

HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus.

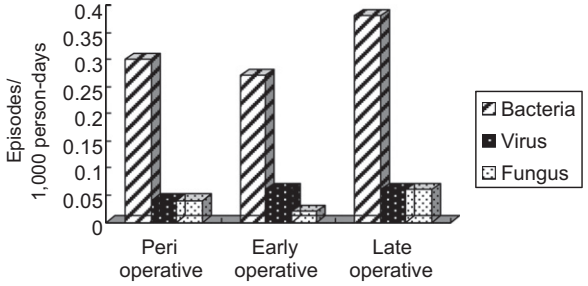

Figure 1. Episodes of infection at different periods after orthotopic liver transplantation.

Table 3 shows the anatomical sites of the bacterial infections. The biliary tract was the most common site (19 episodes, 38.0%), followed by the blood stream (11 episodes, 22.0%), and lower respiratory tract (5 episodes, 10%).

Next, we compared patients with and without bacterial infections (Table 4). Univariate analysis for the risk factors of bacterial infection revealed that the average amount of blood transfusion (which included whole blood, packed RBCs, and frozen fresh plasma) (14,945 mL *vs.* 9,329 mL, $p < 0.01$), pretransplantation serum bilirubin level, retransplant, operation complication, and days of ICU stay were associated with higher rate of bacterial infection. Multivariate analysis revealed that only operation complication had the higher risk for bacterial infection, odds ratio was 16.04 (Table 5).

A total of 16 patients had rejection events after transplantation (biopsy proven in nine patients, seven possible cases), and all of them were given MTP pulse immunosuppressive therapy. Among these 16 patients, there were 13 infection episodes, 2 at 30 days before the rejection event (4.0/1,000 patient-days), and 11 at 30 days after that (22.5/1,000 patient-days). A tacrolimus-based regimen was administered to 48 transplant recipients, and a cyclosporine-based regimen was administered to 20 patients. The bacterial infection rates were similar in these two groups ($p = 0.473$).

Operation-related complications occurred in 13 recipients (19.1%), and these included 10 cases of biliary tract stricture (14.7%), three cases of bile leakage (4.4%), one case of subphrenic hematoma (1.47%), and one case of hepatic artery thrombosis (1.47%). Two patients had stricture and bile leakage. Biliary stricture occurred between Day 9 and Day 453 after OLT (median: 169 days), with 80% of these strictures occurring in the early and late-operative phases. BTI occurred in six patients with biliary tract stricture (60%), and was significantly associated with biliary tract stricture ($p < 0.001$).

Endoscopic biliary stricture dilatation and stent placement was performed for all 10 patients with biliary tract stricture. One of these patients achieved "success", two patients had the status of "under treatment", and seven patients had "failure" (all of whom received PTCD for stricture dilatation and bile drainage), six of whom subsequently developed BTI. None of seven patients who received PTCD achieved "success", three remained in the status of "under

Table 2 Infectious organisms identified in orthotopic liver transplant recipients

	Perioperative period	Early operative period	Late-operative period
Bacteria	16	14	20
Staphylococcus aureus	1	3	0
Pseudomonas aeruginosa	4	1	8
Escherichia coli	6	1	10
Stenotrophomonas maltophilia	1	2	0
Klebsiella pneumoniae	0	2	0
Citrobacter freundii	0	1	0
Acinetobacter baumannii	2	1	0
Streptococcus constellatus	2	0	0
Streptococcus viridans	0	1	1
Peptostreptococcus micros	0	0	1
Enterococcus fecalis	0	2	0
Mycobacterium tuberculosis	0	0	1
CMV	0	0	1
HSV	2	2	0
VZV	0	1	2
Candidiasis	1	0	1
Aspergillosis	1	1	0
Cryptococcosis	0	0	2

CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella-zoster virus.

treatment", two received stent placement at another hospital, and two died. The time from initial stent placement by ERC or catheter placement by PTCD for biliary stricture to BTI was 34.5 days and 33.2 days, respectively.

Sixty-three recipients (92.7%) were followed for more than 1 year (mean: 24.8 months). The 1-year survival rate was 88.8%. Eight patients died during the follow-up period, six patients died within 6 months of transplantation, and one died at 11 months after transplantation. The mortality rate was significantly higher for patients with infections (14% *vs.* 0%, $p < 0.001$), and for patients who received retransplantation (75% *vs.* 7.8%, $p < 0.01$). Figure 2 shows the Kaplan-Meier survival curve of the infected group and noninfected group.

Discussion

Postoperative infection is a well-known problem for liver transplant recipients.[1–5,10] In this study, we found that 29 liver transplant recipients (42.6%) had infectious complications postoperatively and that 78% of these infections were because of bacteria. During the early and late-operative periods, recurrent BTI was the most common cause of bacterial infection (47%), and these infections were associated with biliary tract stricture.

Similar to prior studies,[3,8] we found that bacterial infections were the most common infectious complications (38.2%) in patients receiving OLT. Previous studies have identified several risk factors associated with bacterial infections after OLT, including duration of surgery, amount of blood transfusion, and complications during surgery.[1,8] In our patients, surgical complications—but not duration of surgery and amount of blood transfusion—were also associated with bacterial infections.

There are many risk factors to influence the rate of bacterial infection after liver transplantation.[8]Compared with previous studies,[3,8] our patients had a lower rate of bacterial infection. This difference may be attributed to two major factors: different surgical methods and lower confirmed acute rejection episodes. In earlier reports,[1,3] choledochoduodenal anastomosis was associated with a higher infection rate, possibly because of the disruption of Oddi's sphincter. All of our patients received choledochocholedochal anastomosis

Table 3 Anatomical sites of bacterial infection at three different periods after orthotopic liver transplantation (perioperative: onset within 1 mo; early operative: onset within 1–6 mo; late operative: onset after 6 mo)

	Perioperative	Early operative	Late operative	Total (%)
Bacteremia	5	3	3	11 (22)
Pneumonia or empyema	3	1	1	5 (10)
Urinary tract infection	2	0	2	4 (8)
Peritonitis or intra-abdominal abscess	2	1	1	4 (8)
Liver abscess	1	2	1	4 (8)
Biliary tract infection	3	5	11	19 (38)
Cellulites or wound infection	0	2	1	3 (6)
Total (%)	16 (32)	14 (28)	20 (40)	

Table 4 Univariate risk factors for bacterial infection in orthotopic liver transplant recipients

Univariate Risk factors	With bacterial infection ($n = 26$)	Without bacterial infection ($n = 42$)	p
Age (mean), yr	52.1	50.6	0.54
Gender (male/female)	18/8	28/14	0.82
Pretransplantation laboratory data			
White blood cell, /μL	5,249	5,422	0.81
Hemoglobin, g/dL	11.5	10.7	0.13
Platelet, /μL	85,720	62,370	0.06
Bilirubin, total, mg/dL	14.4	7.0	0.007
Serum GPT, IU/L	266.9	77.5	0.06
Creatinine, mg/dL	1.4	1.1	0.37
Prothrombin time, s	24.8	20.4	0.20
Albumin, g/dL	2.6	2.5	0.77
Elective/urgent transplantation	23/3	39/3	0.48
ICU stay, d	8.5	3.8	0.001
Co-morbidity, patient numbers	10	10	0.19
Operation time, hr	15.5	15.4	0.92
Blood transfusion, mL	14,953	9,458	0.005
Immunosuppression regimen (tacrolimus/cyclosporin)	20/6	27/15	0.473
Rejection (yes/no)	22/4	37/5	0.68
Retransplant (yes/no)	4/22	0/42	0.007
Operation complication, patient numbers	11	2	<0.001

GPT = glutamic pyruvic transaminase.

of the bile duct, a procedure that preserves the function of Oddi's sphincter and decreases the rate of ascending infection from the intestine and resulting bacteremia.[1,3] Lower confirmed acute rejection episodes in this study reduce the MTP bolus for rejection treatment. High-dose MTP treatment of acute rejection will increase the infection episodes, as seen in former studies and this study.[10] So, decreased MTP bolus for acute rejection can reduce the infection episodes in this study than others. Furthermore, culture was not all done when infection was suspected. In this study, episode was collected only when a positive culture result was seen. This underestimated the true bacterial infection episodes.

In other previous studies,[1–3,10] bacterial infection occurred most frequently in the perioperative period; by contrast, we observed no difference in bacterial infection rates during the perioperative, early operative, and late-operative periods. This difference could be because of the occurrence of recurrent BTI, which was more common in the early and late-operative periods. BTI accounted for 47% of all episodes of bacterial infection in our early and late-operative periods (16 episodes), and 14 of these episodes were related to biliary tract stricture. A previous study observed biliary complications in 11–29% of patients receiving liver transplantation,[11] with anastomotic stricture the most common complication.[12,13] We observed biliary tract stricture in 14.7% of our patients, similar to that of other studies of liver transplant recipients (5–17.8%).[12,13] A previous study found that most episodes of biliary tract stricture occurred after 1 month of transplantation,[14] similar to the present study. Furthermore, our data showed that BTI was highly correlated to biliary tract stricture ($p < 0.0001$), and this may explain the higher bacterial infection rates in the early and late-operative periods of our study.

Table 5 Multivariate risk factors for bacterial infection in orthotopic liver transplant recipients

Categories	AOR	Range	p
Operation complication (patient numbers)			
No ($n = 55$)	1 (reference)		
Yes ($n = 13$)	16.04	3.42–75.30	<0.0001
ICU stay	0.97	0.87–1.09	0.636

Adjusted age, sex.
ICU = intensive care unit; AOR = adjusted odds ratio.

Historically, different surgical methods have been used to manage anastomotic biliary stricture.[15] Before the late 1980s, surgical intervention was mostly used to correct transplantation-related biliary tract stricture; since then, percutaneous transhepatic cholangiography or ERC are more widely used. Currently, percutaneous transhepatic cholangiography and ERC have a high success rates (88%).[16] It is currently recommended that the biliary stent be replaced every 3 months;[16] however, based on our findings, the mean time between stent placement and BTI was 34.5 days. Thus, we suggest that ERC be performed more frequently than the current recommendation to prevent biliary tract restenosis. On the other hand, the mean time between PTCD catheter placement to BTI was 33.2 days, so the current recommendation of monthly PTCD revision seems reasonable.[17]

The incidence of TB in liver transplant recipients varies significantly, from 0.35% in developed countries to 15% in endemic areas.[18–21] Most cases of TB occur within 12 months of transplantation, and tend to present as pulmonary TB.[21] In the present study, only one patient (1.5%) had hepatic TB, and this was diagnosed 797 days after

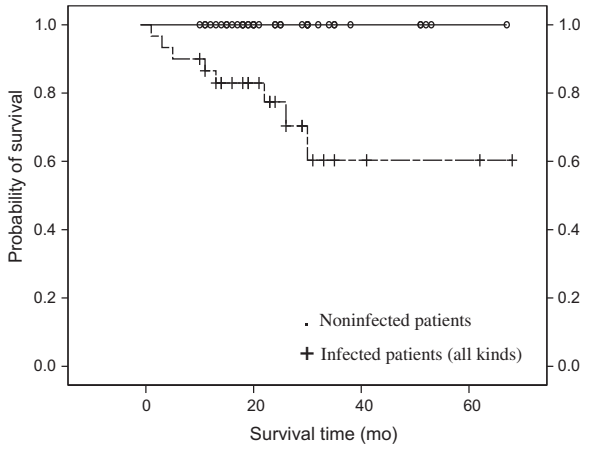

Figure 2. Kaplan-Meier survival curves of infected patients and noninfected patients after orthotopic liver transplantation.

transplantation. The incidence of invasive fungal infections in our patients (8.8%) was similar to that reported in other studies (2—23.8%),[3,5,7,9] and unlike the study,[4] that has high fungal infection rate (42%), which may be because of higher rates of steroid and antimicrobial use before transplantation than other studies. In comparison with other reports,[3—7,22—24] our patients had similar time courses in acquiring invasive fungal infections (first 2 months posttransplantation for *Candida*; first 3 months for *Aspergillus*; after 6 months posttransplantation for *Cryptococcosis*). CMV infection/disease has been reported to occur in 25—80% of liver transplant recipients,[25,26] but we only had one patient with CMV infection. We believe that our low CMV infection rate is an underestimation, because CMV pp65 or DNA analysis was only performed in patients with unexplained elevation of liver enzymes. Furthermore, the time courses of HSV and varicella-zoster virus infections in our patients were similar to those of previous studies,[6,27] although our patients had a lower rate of HSV infection (5.9%, 4/68). However, our HSV oral-labial reactivation rate may also be an underestimate, because culturing for oral lesions was not always performed at the proper times.

Rejection is another important risk factor for infectious complications after liver transplantation.[28] The incidence of acute rejection, including confirmed (9/68, 13.2%) and possible cases (7/68, 10.3%), was 23.5% (16/68), which was similar to other studies.[28—30] MTP pulse therapy plays a major role in suppressing acute rejection, but it has been reported to increase the risk of infection,[10] similar to our observations. Our overall mortality rate was 11.7% (8/68) and the mortality rate of infected patients was 14% (4/29), comparable to those reported previously.[1—3] As described previously,[2,3] retransplantation ($p < 0.001$) and infection ($p < 0.001$), especially invasive fungal infection, were the main risk factors associated with mortality.

There were several limitations to our study. First, our study was retrospective, so the clinical infectious signs and symptoms might be underrecorded. Second, our sample size ($n = 68$) was somewhat small. Third, our study was performed at a single hospital, so the results might not be applicable to other health care facilities in Taiwan. Fourth, culture was not all done when infection was suspected. In this study, episode was collected only when a positive culture result was seen. This underestimated the true bacterial infection episodes.

In conclusion, we found that bacterial infection is the most common infectious disease after liver transplantation. The operation-related complications, especially biliary tract stricture, are important risk factors for bacterial infection. Retransplantation and infections are associated with significantly higher mortality rate in transplant recipients. Our results suggest that the currently recommended time for stent replacement (3 months) should be reevaluated for liver transplant patients.

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