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Predictors and Outcome of Early- versus Late-Onset Major Bacterial Infections in Liver Transplant Recipients Receiving Tacrolimus (FK506) as Primary Immunosuppression

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Major bacterial infections and the predictors of early (within 100 days of transplantation) versus late onset (after 100 days post-transplant) bacterial infections were prospectively assessed in 130 consecutive liver transplant recipients receiving tacrolimus (FK506) as primary immunosuppression. The median follow-up period was 38 months. Overall, 35% (45/130) of the patients developed 67 episodes of major bacterial infections (0.52 episodes/patient). Sixty-three percent of the major bacterial infections occurred early, and 37% occurred in the late post-transplant period. Eighty-four percent of the abdominal infections occurred early, whereas 38% of the cases of pneumonia, 60% of the cases of primary bacteremia, and 50% of the biliary infections occurred late. By logistic regression analysis, portal vein thrombosis was the most significant independent risk factor for early-onset major bacterial infection (odds ratio 4.1; 95% CI 1.4–12.2), and recurrent hepatitis C was the most significant independent predictor of late-onset major bacterial infections (odds ratio 6.21; 95% CI 1.9–20.2). Thus, sources and risk factors differ for early versus late-onset bacterial infections after liver transplantation. Knowledge of the differences in the potential sources, the pathogens, and the predictors of early versus late-onset bacterial infections can be valuable in the evaluation and empiric treatment of liver transplant recipients with bacterial infections.

Bacterial infection remains the most frequently occurring infectious complication of liver transplantation (1–7). Although the vast majority of such infections occur within the first three months post-transplantation, significant disease may still be encountered more than three months after transplantation. Cytomegalovirus (CMV) infection, prolonged operation time, blood loss, prior hepatobiliary surgery, and Roux-en-Y anastomosis have been proposed as risk factors for development of bacterial infections after liver transplantation (1, 2, 4).

Pretransplant and operative variables are not relevant predictors of late-onset bacterial infections, since conditions present at the time of the operation may not be accurate predictors of infections that occur many months later. Furthermore, while the epidemiology and risk factors for post-transplant bacterial infections in liver transplant recipients receiving cyclosporine have been described previously, a detailed analysis focusing specifically on bacterial infections in liver transplant recipients receiving tacrolimus (FK506) has not been reported to our knowledge. Tacrolimus is several hundredfold more potent in its immunosuppressive effect than cyclosporine; however, the requirement of adjunctive immunosuppression, e.g., corticosteroids, is lower with tacrolimus (8, 9). In the prospective study herein, we summarize the major bacterial infections (early and late) and the differential risk factors for their development in liver transplant recipients receiving tacrolimus as primary immunosuppression.

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Table 1: Demographic characteristics of the study patients.

No. of patients	130
Mean age in years (range)	47 (22–69)
Underlying liver disease[a]	
Hepatitis C	53%
Alcoholic cirrhosis	45%
Hepatitis B	9%
Primary sclerosing cholangitis	10%
Hepatocellular carcinoma	5%
Cryptogenic cirrhosis	4%
Metabolic liver disease	4%
Primary biliary cirrhosis	2%
UNOS score[b]	
4	32%
3	66%
2	2%

[a] Some patients had more than one underlying liver disease.
[b] UNOS status shown is the one used prior to 1 April 1995: UNOS 1, stable patient awaiting transplantation at home; UNOS 2, waiting at home requiring medical support; UNOS 3, unstable, in need of continuous hospitalization; UNOS 4, requiring life support system.
UNOS, United Network of Organ Sharing.

Patients and Methods

At a newly established liver transplant program at the Pittsburgh VA Medical Center, consecutive patients undergoing liver transplantation were prospectively followed for development of infection. Between October 1989 and October 1995, 130 consecutive adult patients underwent liver transplants and comprised the study population.

Immunosuppression. All patients received tacrolimus and low-dose prednisone as immunosuppressive agents. One gram of methylprednisolone was given immediately after revascularization of the graft. Twenty milligrams of methylprednisolone was given i.v. daily until the oral route was established, when 20 mg of prednisone was administered daily. During the subsequent months, the prednisone dose was slowly tapered. Rejection episodes were treated with 1 g of methylprednisolone bolus with or without steroid cycles (methylprednisolone given i.v. in 4 divided doses daily, tapering the dose from 200 mg to 20 mg per day over 6 days). OKT3 was used for steroid-resistant rejection.

Table 2: Major bacterial infections stratified by the timing of onset post-transplantation.

Infection	No. occuring ≤ 100 days	No. occuring > 100 days	Total
Pneumonia	8	8	16
Primary bacteremia	9	6	15
Intra-abdominal infection	10	2	12
Peritonitis	(5)	(1)	(6)
Subhepatic abscess	(3)	(1)	(4)
Hepatic abscess	(2)	(0)	(2)
Colitis	6	4	10
Wound/skin infections	5	2	7
Cholangitis	3	3	6
Joint infection	1	0	1
Total	42	25	67

Antimicrobial Prophylaxis. Perioperative prophylaxis consisted of ampicillin and cefotaxime for 24 h. Patients allergic to penicillin received clindamycin and aztreonam. Trimethoprim/sulfamethoxazole was used indefinitely as *Pneumocystis* prophylaxis. Aerosolized pentamidine was substituted in patients allergic to or unable to tolerate trimethoprim/sulfamethoxazole. Selective bowel decontamination was performed during the initial post-transplant intensive care unit (ICU) stay by employing 24 ml of MUD mixture (colistin 100 mg/20 ml, gentamicin 80 mg/20 ml, and nystatin 2 million units/20 ml) orally or via nasogastric tube four times daily. Acyclovir, 600 mg daily, was administered for one month after transplantation as herpes simplex virus prophylaxis. Preemptive ganciclovir for seven days (upon CMV shedding) was employed as prophylaxis for CMV disease (10).

Definition of Infection. Infection was defined using criteria proposed by the Centers for Disease Control and as reported previously (2, 3, 11). Major bacterial infections included bacteremia, intra-abdominal abscesses, wound infections, peritonitis, pneumonia, *Clostridium difficile* colitis, cholangitis, septic arthritis, and skin and soft tissue infections (3). Primary bacteremia was defined as catheter-related bacteremia or bacteremia of unknown source (11). Cytomegalovirus infection and CMV disease were defined as reported previously (10).

Risk Factors for Bacterial Infection. The following variables were assessed as risk factors for bacterial infection in our patients: (i) pretransplant variables, including age, sex, underlying liver disease, Child-Pugh score, United Network of Organ Sharing (UNOS) score, serum bilirubin, serum creatinine, requirement of dialysis, pretransplant use of antibiotics (within 4 weeks of transplantation), ICU stay at any time prior to transplantation, duration of ICU stay; (ii) operative variables, including donor age, donor sex, cold ischemic time, duration of transplant surgery, portal vein thrombosis (of 30 patients with portal vein thrombosis in this study, 24 had mural thrombi detected during surgery and clotted portal vein documented by imaging studies pretransplant), type of duct anastomosis, and number of packed red blood cells transfused; (iii) post-transplant variables, including antibiotic use (within 4 weeks of transplantation, excluding the prophylactic regimen), length of post-transplant ICU stay, readmission to the ICU, number of abdominal and intrathoracic operations, dialysis, histopathologically documented recurrence of hepatitis C virus (HCV) hepatitis, retransplantation, CMV infection, CMV disease, biopsy-proven rejection, number of steroid boluses and recycles used, and the use of OKT3.

Bacterial infections were considered early if they occurred within 100 days of transplantation and late if they occurred after 100 days (12, 13). The risk factor analysis was stratified by early and late-onset bacterial infection (12). Pretransplant and operative variables were included only in the analysis of early bacterial infections (12). Post-transplant variables assessed as risk factors for early bacterial infection included antibiotic use (other than prophylaxis), length of ICU stay, retransplantation, repeat abdominal or thoracic surgery, dialysis, CMV infection, CMV disease, rejection, and additional immunosuppression; only those events occurring prior to bacterial infection were construed as risk factors. Post-transplant variables assessed as risk factors for late bacterial infection included: age, underlying liver disease, donor age, requirement of dialysis, retransplantation, rejection, additional immunosuppression, CMV infection, and CMV disease. Recurrent HCV hepatitis was diagnosed based on histologic criteria de-

Table 3: Risk factors for early post-transplant bacterial infections (univariate analysis).

Variable	Patients with early infections (n = 33)	All other patients (n = 97)	P value
Pretransplant variables			
Mean age (years)	48.7	46.6	NS
Underlying liver disease			
Hepatitis C	57%	54%	NS
Hepatitis B	6%	10%	
Alcoholic cirrhosis	48%	41%	
Other	15%	15%	
Mean Child-Pugh score	12.0	11.4	NS
UNOS score			
2	0%	3%	NS
3	67%	66%	
4	33%	31%	
Mean serum bilirubin (mg/dl)	4.0	6.4	NS
Mean serum creatinine (mg/dl)	1.6	3%	NS
Pretransplant dialysis	6%	3%	NS
Pretransplant antibiotics (within 4 weeks)	30%	27%	NS
Operative variables			
Mean operation time (h)	12.8	12.1	NS
Mean cold ischemic time (h)	13.7	13.3	NS
Mean blood loss (units)	18.6	18.7	NS
Mean donar age (years)	35.3	31.9	NS
Portal vein thrombosis	39%	18%	0.011
Roux-en-Y anastomosis	48%	47%	NS
Post-transplant variables			
Mean length of ICU stay (days)	19.7	7.1	0.005
Readmission to ICU	64%	21%	0.0001
Repeat intra-abdominal or intrathoracic surgery	42%	18%	0.004
Post-transplantation dialysis	36%	8%	0.0005
Retransplantation	12%	6%	NS
Mean no. of rejection episodes	0.8	0.4	0.05
Mean no. of steroid boluses	1.0	0.4	0.007
Mean no. of steroid recycles	0.5	0.2	0.02
CMV infection	33%	31%	NS
CMV disease	18%	10%	NS

CMV, cytomegalovirus; ICU, intensive care unit; NS, not significant; UNOS, United Network of Organ Sharing.

fined previously, which included portal lymphoid follicles, mononuclear lobular infiltrate, and hepatocyte necrosis with degeneration and ballooning in the absence of CMV, Epstein-Barr virus, herpes simplex virus, hepatitis B virus, and rejection in a patient undergoing liver transplantation for endstage liver disease due to HCV (14).

Statistical Analysis. Demographics and laboratory values were entered into a database (Prophet Statistics, BBN Systems and Technologies, USA). Patients with and without post-transplant fungal infections were compared as follows: continuous variables (age, bilirubin, serum creatinine, duration of ICU stay, Child-Pugh score, cold ischemic time, etc.) were compared using the *t* test or, when a normal distribution could not be assumed, the Mann-Whitney test. Categorical data (underlying liver disease, presence or absence of CMV, dialysis, antibiotic use, etc.) were compared using the chi-square or Fisher's exact test. For patients undergoing early retransplantation (within 100 days), the initial transplant was used to assess baseline variables (13). For late retransplantation (after 100 days), the variables at retransplant were used for analysis.

Results

Characteristics of the Study Population. Of 130 consecutive patients that comprised the study sample, 98% (128/130) were male. The demographic features of these patients are shown in Table 1. Eight percent (10/130) of the patients were retransplanted. The actuarial patient survival was 90% at six months, 87% at 12 months, 85% at 22 months, and 80% at 60 months. Patients were followed until death; the median follow-up period for the living patients was 38 months (range, 3 to 74 months).

Incidence and Types of Major Bacterial Infections. Overall, 35% (45/130) of the patients developed 67 episodes of major bacterial infections (0.52 episodes/patient). Sixty-seven percent (67/100) of the major infections occurring during the study period were due to bacteria.

Pneumonia, documented in 24% (16/67) of the episodes, was the most frequently encountered major bacterial infection in our patients (Table 2). Twenty-five percent (4/16) of the episodes of pneumonia were due to enteric gram-negative bacteria, 13% (2/16) to *Legionella*, 13% (2/16) to *Pseudomonas aeruginosa*, 6% (1/16) to *Mycobacterium tuberculosis*, and 6% (1/16) to *Haemophilus influenzae*. Methicillin-resistant *Staphylococcus aureus* accounted for 13% (2/16) of pneumonia cases. The etiologic agent of pneumonia was undetermined in 25% (4/16) of the cases; however, in all of these cases the patients responded to broad-spectrum antibiotics employed empirically to treat their pulmonary infection. Nineteen percent (3/16) of the cases of pneumonia were accompanied by empyema; these included one case each of *Legionella*, *Serratia marcescens*, and *Citrobacter freundii* pneumonia. Only 19% (3/16) of the episodes of pneumonia were accompanied by bacteremia; these included one episode due to *Escherichia coli*, one due to *Enterobacter cloacae*, and one due to methicillin-resistant *Staphylococcus aureus* (MRSA).

Primary bacteremia occurring in 22% (15/67) of the episodes was the second most frequently encountered bacterial infection in our patients. Eighty-seven percent (13/15) of the cases of primary bacteremia were catheter related, of which MRSA was the predominant etiologic agent

Table 4: Logistic regression analysis of variables associated with early post-transplant bacterial infections.

Variable	P value	Odds ratio	95% CI
Portal vein thrombosis	0.011	4.1	1.4–12.2
Length of ICU stay	0.014	1.05	1.01–1.10
Additional immuno-suppression	0.023	3.4	1.2–9.7
Post-transplant dialysis	0.103	2.9	0.8–10.8
Rejection episodes	0.487	1.17	0.75–1.8
Repeat surgery	0.888	1.1	0.34–3.4

CI, confidence interval; ICU, intensive care unit.

(58%, 7/13). Bacteremia of unknown source, documented in 13% (2/15) of patients, was due to *Pseudomonas* spp. in both cases.

Intra-abdominal infections (6 abscesses, 6 cases of peritonitis) were observed in 18% (12/67) of the patients (Table 2). Hepatic abscesses (n = 2) were secondary to hepatic artery thrombosis in both cases; the etiologic pathogens were *Citrobacter freundii* in one case and *Enterococcus faecalis* plus *Candida* spp. in the other case. Bacteremia was observed in 17% (2/12) of the patients with intra-abdominal infections (due to MRSA in 1 case and *Citrobacter freundii* in the other). Biliary infections occurred in 9% (6/67) of the episodes and were associated with bacteremia in 66% (4/6) of the cases. Enterococci and *Pseudomonas aeruginosa* were the predominant pathogens in biliary tree infections. *Clostridium difficile* colitis constituted 13% (9/67) of the bacterial infections. Colitis due to *Yersinia enterocolitica* was documented in one case. Wound infections were observed in 10% (7/67) of the cases and were predominantly due to MRSA (57%, 4/7 cases). Fifty-seven percent (4/7) of the wound infections were associated with bacteremia.

Table 5: Factors associated with late post-transplant bacterial infections (univariate analysis).

Variable	Late infections (n = 22)	All other patients (n = 96)	P value
Mean age (years)	47.0	47.0	NS
Underlying liver disease			
Hepatitis C	79%	52%	0.03
Hepatitis B	0%	10%	
Alcoholic cirrhosis	42%	42%	
Other	5%	18%	
Mean donor age (years)	37.9	31.3	NS (0.08)
Dialysis	32%	7%	0.007
Retransplantation	5%	6%	NS
Mean rejection episodes/patient	1.1	0.4	0.004
Mean no. of steroid boluses	1.8	0.3	0.0005
Mean no. of steroid recycles	0.4	0.2	NS (0.08)
CMV infection	47%	31%	NS
CMV disease	21%	12%	NS
Recurrent HCV hepatitis	68%	22%	0.0001

CMV, cytomegalovirus; HCV, hepatitis C virus; NS, not significant, p > 0.05.

Timing of Onset of Infections. A vast majority of the abdominal infections occurred in the early post-transplant period (within the first 3 months): 83% (5/6) of the intra-abdominal abscesses, 66% (4/6) of the episodes of peritonitis, and 100% (7/7) of the wound infections were early-onset infections. On the other hand, primary bacteremia, pneumonia, and biliary infections frequently occurred in the late post-transplant period: 38% (6/16) of the cases of pneumonia, 60% (9/15) of the episodes of bacteremia, and 50% (3/6) of the biliary infections were late-occurring infections.

Risk Factors for Early versus Late Infections. By univariate analysis, portal vein thrombosis (p = 0.011), length of post-transplant ICU stay (p = 0.005), readmission to the ICU (p = 0.0001), repeat intra-abdominal or intrathoracic surgery (p = 0.004), and post-transplant dialysis (p = 0.0005) were significantly associated with early bacterial infections (Table 3). By logistic regression analysis, portal vein thrombosis (p = 0.011; odds ratio, 4.1; 95% CI, 1.4–12.2) was the most significant independent predictor of early bacterial infections (Table 4). Of the 16 episodes of bacterial infections in patients with portal vein thrombosis, 50% (8/16) were intra-abdominal infections (peritonitis 3, intra-abdominal abscess 2, cholangitis 2, colitis 1); 25% (4/16) were bacteremia (*Pseudomonas* spp. 2, enterococcus 1, *Staphylococcus aureus* 1); 19% (3/16) were pneumonia; and 6% (1/16) were wound infection. Other factors independently associated with early bacterial infection were length of post-transplant ICU stay (p = 0.014) and additional immunosuppression (p = 0.023).

Factors associated with late bacterial infections by univariate analysis were recurrent HCV hepatitis (p = 0.0001), post-transplant dialysis (p = 0.007), and corticosteroid boluses (p = 0.0005) (Table 5). By logistic regression analysis, HCV recurrence (p = 0.002) and additional immunosuppression (p = 0.01) were independently significant predictors of late bacterial infections (Table 6). Infections in patients with recurrent HCV hepatitis included pneumonia, *Clostridium difficile* colitis, abdominal abscess, peritonitis, and primary bacteremia.

Mortality. Forty-four percent (20/45) of the patients with major bacterial infections died, compared with 7% (6/85) of those without major bac-

Table 6: Logistic regression analysis of variables associated with late post-transplant infections.

Logistic	P value	Odds ratio	95% CI
HCV recurrence	0.0025	6.21	1.90–20.27
Additional immuno-suppression	0.0146	4.68	1.36–16.17
Donor age	0.101	1.03	0.99– 1.07
Rejection	0.39	1.24	0.75– 2.06
Dialysis	0.34	216	0.45–10.49

CI, confidence interval; HCV, hepatitis C virus.

terial infections (p = 0.0001). Mortality was 36% (12/33) in patients with early bacterial infections, compared with 58% (11/19) in those with late bacterial infections (p = NS).

Discussion

Thirty-five to 70% of the liver transplant recipients receiving cyclosporine have experienced at least one episode of major bacterial infection (2, 4, 6, 7, 15, 16). The incidence of such infections reported in the literature ranges between 0.79 and 1.46 episodes per patient (2, 4, 6, 16). In our study 35% (45/130) of the consecutive liver transplant recipients receiving tacrolimus had 67 episodes of major bacterial infection, for an incidence of 0.52 episodes per patient.

Portal vein thrombosis was the most significant independent predictor of early-onset major bacterial infection after liver transplantation in our patients. To our knowledge this finding has never been reported previously. Portal vein thrombosis is a well-recognized complication of cirrhosis, occurring in 2 to 15% of liver transplant recipients (17, 18). It is believed to result from intimal injury along with elevated portal vein pressure. Once considered an absolute contraindication to liver transplantation, it is no longer deemed so (17). We have previously reported a very high incidence of portal vein thrombosis in our liver transplant recipients; 26% of 88 consecutive patients at our institution had preoperative or unexpected portal vein thrombosis detected intraoperatively (17, 18). Although graft survival was lower, no difference in patient survival was observed between patients with and without portal vein thrombosis (18). Other institutions have reported similar findings (17).

Several factors may account for a higher incidence of infectious morbidity in patients with portal vein thrombosis, which is often regarded as a surrogate for advanced liver disease (17). Technical factors and the difficult intraoperative course of these patients may also be a contributory variable. "Wooden hilum" and engorged vessels make dissection difficult (17, 18).

The first three months post-transplantation are believed to be the period associated with greatest risk of bacterial infection after liver transplantation. Indeed, 79 to 85% of bacterial infections reported previously have occurred in the first three months (2, 4, 5, 16). Requirements of ICU stay, mechanical ventilation, and intravascular access are believed to predispose these patients to bacterial infection in the early post-transplant period. It is noteworthy that 37% of the major bacterial infections in our study occurred after three months. Furthermore, mortality rates of late- (58%) and early-onset bacterial infections (36%) were similar. Thus, late-occurring bacterial infections were an equally significant source of morbidity and mortality in our patients as the early-onset major bacterial infections.

Recurrent HCV hepatitis was identified as the most significant independent predictor of late-onset infection in our patients; the risk of late-onset bacterial infection in patients with HCV recurrence was sixfold higher than in all other patients. It is believed that HCV is an immunosuppressive and immunomodulatory virus (19). A number of reports have documented the overall increased propensity of liver and renal transplant recipients to develop infectious complications (12, 20, 21). In a recent study of renal transplant recipients, the incidence of infection (84% vs. 75%, p = 0.05) and the number of episodes of infection per patient (5.7 vs. 3.9, p = 0.002) were higher in patients with chronic viral hepatitis as compared with other patients (21). Patients with hepatitis had a significantly higher number of bloodstream, pulmonary, and central nervous system infections (21). A higher incidence of infection in liver transplant recipients with HCV could also be due to recurrence of liver disease with its attendant complications, e.g., ascites and the need for hospitalization. Although a significant difference in five-year survival between patients with and without HCV recurrence has not been demonstrated (22), our data suggest that patients with HCV recurrence have significant morbidity due to infections in the late post-transplant period.

Our main conclusions may therefore be stated as follows. Sixty-three percent of the major bacterial infections occurred within three months of

transplantation. An overwhelming majority of the abdominal infections occurred early, whereas pneumonia, primary bacteremia, and biliary infections occurred frequently in the late post-transplant period. Our data further show that patients with portal vein thrombosis, now an acceptable indication for liver transplantation at many centers, are at a fourfold higher risk of developing early-onset major bacterial infections; portal vein thrombosis was identified as the most significant independent predictor of these infections. Finally, HCV hepatitis has emerged as a major indication for orthotopic liver transplantation. Although a significantly adverse impact on survival has not been documented, our data show that patients with hepatitis C are at sixfold higher risk of late-occurring major bacterial infections than other patients.

References

1. Winston DJ, Emmanouilides C, Busuttil RW: Infections in liver transplant recipients. Clinical Infectious Disease 1995, 21: 1077–1091.
2. Kusne S, Dummer JS, Singh N, Iwatsuki S, Makowka L, Esquirel C, Czechs AG, Starzl TE, Ho M: Infections after liver transplantation, an analysis of 101 consecutive cases. Medicine 1988, 67: 132–143.
3. Singh N, Gayowski T, Wagener M, Yu VL: Infectious complications in liver recipients on tacrolimus: prospective analysis of 88 consecutive liver transplants. Transplantation 1994, 58: 774–778.
4. Mora P, Gonwa TA, Goldstein R, Husberg BS, Klintmalm GB: Risk factors of postoperative infection after liver transplantation: a univariate and stepwise logistic regression analysis of risk factors in 140 consecutive patients. Clinical Transplantation 1992, 46: 443–449.
5. Paya CV, Hermans PE, Washington JA, Smith TF, Anhalt JP, Wiesner RH, Krom RAF: Incidence, distribution and outcome of episodes of infection in 100 orthotopic liver transplantations. Mayo Clinic Proceedings 1989, 64: 555–564.
6. Lumbreras C, Lizasoain M, Moreno E, Agaudo JM, Gomez R, Garcia I, Gonzoles I, Loinaz C, Cisneros C, Noriega AR: Major bacterial infections following liver transplantation. Hepatology-Gastroenterology 1992, 39: 362–365.
7. Wade JJ, Rolando N, Hallar K, Philpott-Howard J, Casewell MW, Williams R: Bacterial and fungal infections after liver transplantation: an analysis of 284 patients. Hepatology 1995, 21: 1328–1366.
8. European FK506 Multicenter Liver Study Group: Randomized trial comparing tacrolimus (FK506) and cyclosporine in prevention of liver allograft rejection. Lancet 1994, 344: 423–428.
9. The U.S. Multicenter FK506 Liver Study Group: A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. New England Journal of Medicine 1994, 332: 1110–1115.
10. Singh N, Yu VL, Mieles L, Wagener MM, Miner RC, Gayowski T: High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients, a randomized trial. Annals of Internal Medicine 1994, 120: 375–381.
11. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: CDC definitions of nosocomial infections. American Journal of Infection Control 1988, 16: 128–140.
12. Singh N, Gayowski T, Wagener MM, Doyle H, Marino IR: Invasive fungal infections in liver transplant recipients receiving tacrolimus as primary immunosuppressive agent. Clinical Infectious Diseases 1997, 24: 179–184.
13. Collins LA, Samore MH, Roberts MS, Luzzati R, Jenkins RL, Lewis WD, Karchmer AW: Risk factors for invasive fungal infections complicating orthotopic liver transplantation. Journal of Infectious Diseases 1994, 170: 644–652.
14. Singh N, Gayowski T, Ndimbie OK, Nedjar S, Wagener MM, Yu VL: Recurrent hepatitis C virus hepatitis in liver transplant recipients receiving tacrolimus: association with rejection and increased immunosuppression after transplantation. Surgery 1996, 119: 452–456.
15. Colonna JO, Winston DJ, Brill JE, Goldstein LI, Hoff MP, Hiatt JR, Quinones-Baldrish W, Ramming KP, Bussutil RW: Infectious complications in liver transplantation. Archives of Surgery 1988, 123: 360–364.
16. George DL, Arnow PM, Fox AS, Baker AL, Thistlewaite JR, Emond JC, Whitington PF, Broelsch CE: Bacterial infection as a complication of liver transplantation: epidemiology and risk factors. Reviews of Infectious Disease 1991, 13: 387–396.
17. Seu P, Shackleton CR, Shaked A, Imagawa DK, Olthoff KM, Rudich SR, Kinkhabwala M, Busuttil R: Improved results of liver transplantation in patients with portal vein thrombosis. Annals of Surgery 1996, 131: 840–845.
18. Gayowski T, Marino IR, Doyle HR, Echeverri L, Todo S, Wagener MM, Singh N, Yu VL, Fung JJ, Starzl TE: A high incidence of native portal vein thrombosis in veterans undergoing liver transplantation. Journal of Surgical Research 1996, 60: 333–338.
19. Fishman JA, Rubin RH, Koziel MJ, Periera BJG: Hepatitis C virus and organ transplantation. Transplantation 1996, 62: 147–154.
20. Singh N, Gayowski T, Wagener MM, Marino IR: Increased infections in liver transplant recipients with recurrent hepatitis C virus hepatitis. Transplantation 1996, 61: 402–406.
21. Rao KV, Ma J: Chronic viral hepatitis enhances the risk of infection but not acute rejection in renal transplant recipients. Transplantation 1996, 62: 1765–1769.
22. Gane EJ, Portman BC, Naumov NV, Smith HM, Underhill JA, Donaldson PT, Maertens G, Williams R: Long-term outcome of hepatitis C infection after liver transplantation. New England Journal of Medicine 1996, 334: 815–820.