Infectious complications of liver transplantation

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Sixteen (50%) of the 32 patients who received liver transplantations from October 1991 to March 1993 at Queen Mary Hospital, Hong Kong, developed viral, bacterial, or fungal infections. The viral infections were largely a result of immunosuppression while accidental bowel perforation, bile leak at the anastomosis, and delayed onset of stricture of the bile duct anastomosis were responsible for the intra-abdominal bacterial or fungal infections. Although the incidence of infectious complications was high, all patients were managed effectively and only one patient with lymphoproliferative disorder died. Infectious complications can lead to a prolonged hospital stay and a substantially increased hospital cost. The adoption of new immunosuppressive regimens that can better prevent acute graft rejection and adherence to meticulous surgical technique will help to reduce the infectious complications of liver transplantation in the future.

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Introduction

Liver transplantation is an established treatment method for patients with terminal liver failure. A one-year survival rate of 85% has been achieved in many transplant centres in the world.[1] Infectious complications remain common and are a major challenge for the clinicians and microbiologists looking after these patients. The high incidence of infectious complications stems from the fact that liver transplantation is usually performed in patients who have had multiple previous operations, bleeding diathesis, and portal hypertension. Inadvertent injury to the bowel and haematoma are significant predisposing factors that may lead to intra-abdominal sepsis. Because many of these patients are malnourished and are immunosuppressed or have concurrent immunomodulating viral infections, they run considerable risk of dying from infectious complications. In this report, we review our experience in the management of the infectious complications that occurred in patients receiving liver transplantation at Queen Mary Hospital, Hong Kong.

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Subjects and methods

From October 1991 to March 1996, 33 liver transplantations were carried out in 32 patients. Twenty-three adults and nine paediatric patients received grafts from living relatives (12 patients) or from brain stem-dead patients (21). All patients were screened pre-operatively by haematological and biochemical studies, viral serology for pre-existing hepatitis B virus (HBV), hepatitis C virus, cytomegalovirus (CMV), Epstein-Barr virus, and human immunodeficiency virus (HIV) and given a chest X-ray to detect past or current pulmonary infection. Cultures of swabs of the pharynx and nasal orifice and urine were grown to exclude colonisation by multiresistant bacteriae. Patients with possible spontaneous bacterial peritonitis had paracentesis performed and ascites cultured.

Patients with HBV-induced cirrhosis were accepted for transplantation on a selective basis. The first patient in our series received HBV immune globulin cover[2] after the transplantation. Two patients received lamivudine[3] before and after liver transplantation.

Just before the operation, the patient received a pHisoDerm shower and nystatin cream was applied to skin creases, such as the axillae, groin, and elbows. Chlorhexidine (12%) mouth washes (5-15 mL) were given for oral decontamination. Nystatin suspension, 0.5 mL (50 000 U) /kg/day in four doses were also given. Ampicillin, 50 mg/kg/dose and ceftazidime, 30 mg/kg/dose were given at the time of induction. The

antibiotics were repeated every four to six hours afterwards in the operating theatre. At the time of operation, liver explant biopsy, intestinal contents, or bile contaminating the peritoneal cavity were sent immediately for bacterial and fungal culture.

Post-operatively, mechanical ventilation was instituted in all patients; extubation was initiated when the patient's respiratory effort was satisfactory. Each patient received daily oral toilet with 12% chlorhexidine, nystatin, 0.5 ml/kg/day in four doses via a nasogastric tube, and acyclovir, 10 mg/kg/dose three times daily (orally) for prophylaxis against herpes virus. Intravenous co-trimoxazole (Septrin) 15 mg/kg every 12 hours was also given for prophylaxis against *Pneumocystis carinii* pneumonia. In the paediatric patients, immunoglobulin (GammaGard, Baxter, California, USA) 400 mg/kg/dose weekly for four doses was also given. When a patient underwent liver biopsy or cholangiography, ampicillin, 50 mg/kg every six hours and ceftazidime, 30 mg/kg every six hours was given for two days. Cultures from endotracheal aspirate, urine, drain, wound site, and bile were performed twice weekly.

When the recipient developed fever (>38.5°C), cultures of blood from a central venous line, and peripheral vein and cultures from body fluid were obtained for viral, bacterial, and fungal investigations. When a T-tube had been capped, it was released to drain into a bag and bile obtained for culture. A doppler ultrasound was performed to look for patency of the hepatic artery, portal vein, fluid collection, and any abnormality within the liver. A cholangiogram was performed to detect leakage from the anastomosis or stricture of the bile duct. In the absence of infection in the abdominal cavity, an echocardiogram was performed to check for evidence of endocarditis. Peripheral blood leucocytes from heparinised blood were collected weekly for three months for assays of CMV pp65 antigens and DNA by indirect immunofluorescent test and polymerase chain reaction. When a patient developed persistent pneumonic changes that did not respond to broad spectrum coverage, a bronchoalveolar lavage was performed to exclude pneumonitis due to CMV, respiratory viruses, fungi, bacteriae, mycobacteriae, and *Pneumocystis carinii*.

An infective episode was defined as the presence of a local and/or systemic inflammatory response together with a positive result on microbiological testing by either culture, antigen, or DNA detection from a normally sterile body fluid/tissue or other relevant anatomical site as indicated by clinical or radiological signs.

Antimicrobial therapy including intravenous ceftazidime and co-amoxiclav (Augmentin) were initiated empirically if a patient developed the systemic inflammatory response syndrome after sepsis work-up was performed. The regimen was then modified according to the gram smear, culture, and sensitivity test results (when available).

Table 1. Seroactivity of the donors and their recipients who developed Cytomegalovirus infection post-transplantation

CMV Seroactivity		Treatment
Recipient	Donor	
CMV+	CMV+	ganciclovir, foscarnet
CMV-	CMV+	ganciclovir
CMV+	(not available)	ganciclovir

Results

Twenty seven (84%) patients are alive. The cause of mortality in five patients was primary graft nonfunction (n=1), persistent graft rejection (n=1), portal vein thrombosis (n=1), intracerebral bleeding (n=1), and myocardial infarction (n=1). Sixteen patients (50%) developed one or more infectious complications, which did not contibute directly to mortality.

Viral infections: pre- and post-transplantation

Pre-operative screening showed that 26 donors and 26 recipients were seropositive for CMV. Information on seroactivity for CMV was not available for two donors and two recipients. Matching of seroactivity of donor and recipient showed that 21 pairs were both CMV positive, four pairs were donor CMV positive/recipient CMV negative, and four pairs were donor CMV negative/recipient CMV positive. Three of the recipients developed CMV infection, one after treatment for acute graft rejection. Their pre-operative CMV seroactivity and that of their donors are shown in Table 1. Treatment with ganciclovir was successful in two patients. The third patient required foscarnet for adequate control.

Parainfluenza and influenza pneumonitis occurred in two children (Table 2). They were well after inhaling ribavirin and being given supportive treatment. One adult patient developed herpes zoster but recovered after treatment with acyclovir. One paediatric patient developed hepatitis of unknown aetiology and the

hepatitis eventually led to graft failure. It was necessary to repeat the transplantation using a living graft from her mother. One adult patient developed malignant lymphoma in his new liver. Epstein-Barr virus was found within the tumour and a high level of IgG against EBV viral capsid antigen was also detected. He did not have a history of having received OKT3 and anti-lymphocyte globulin. This patient subsequently died of malignancy. Three patients were hepatitis B surface antigen (HB_s) positive before liver transplantation. The first patient received HBV immune globulin in the post-operative period. He died from primary graft nonfunction and intracerebral bleeding 32 days after the operation. The second and third patients with HBV received lamivudine for more than 30 days before transplantation. Both were rendered HBV DNA-negative before transplantation. The HB_e and HB_s of the second patient disappeared after transplantation. She is still alive and free from recurrence of hepatitis. The third patient died from graft failure secondary to portal vein thrombosis but before death, his HB_e was also rendered negative.

Bacterial and fungal infections: pre- and post-transplantation

Thirteen patients developed bacterial and/or fungal infections (Table 2). Technical error was responsible for the intra-abdominal septic complications in six patients. The intra-abdominal infections were characterised by growth of multiple species and sometimes antibiotic-resistant bacteria. Re-laparotomy and correction of defects were performed for final control of sepsis due to bowel perforation or biliary leakage. In the three cases of acute cholangitis due to delayed onset of biliary stricture at the anastomoses, surgical correction was required in one patient. The other two patients were managed successfully by percutaneous balloon dilatation of the strictures. One patient had insidious onset of colo-vesical fistula secondary to acute diverticulitis of the colon four months after liver transplantation. His initial and only presentation was persistent urinary tract infection. He was well after a sigmoid colectomy and repair of the urinary bladder defect was performed.

Discussion

Despite a high incidence of infectious complications in our series, none of the patients died directly from these complications. This success is a result of the combined efforts of clinicians, microbiologists, pathologists, radiologists, and ICU nurses. The overall success also results from the adoption of prophylactic protocols, early recognition of infection, and aggressive treatment.

The overall success of liver transplantation depends on the liver graft function, which in turn depends on a meticulous effort to avoid graft injury, and good technique in vascular and biliary reconstruction.[4] Primary graft non-function is the worst scenario. Although the exact cause is not known, it is likely multifactorial, and results mainly from the use of a graft that has had prolonged hypotension before harvesting and a very long cold ischaemia after harvesting. Primary graft non-function leads to liver failure and immunodeficiency predisposing the patient to obtundation, aspiration, prolonged endotracheal intubation, ventilator-associated bronchopneumonia, and sepsis in other parts of the body.[4]

After the occurrence of primary graft non-functioning in the second patient in the series, we have been very cautious in the selection and screening of donors so that those with a history of prolonged hypotension are not included. The screening of donors for the presence of concurrent viral diseases such as HBV, hepatitis C, and HIV is necessary to prevent such infections being transmitted to the patient. Cytomegalovirus screening results are informative when the possibility of CMV infection arises in the post-operative period. The presence of septicaemia in a donor precludes organ donation since bacteria may be transferred to the recipient and infect the vascular anastomoses, producing a mycotic aneurysm.[5] Intra-operatively, we exercised meticulous haemostasis, careful preparation of the bile duct, thorough scrutiny for possible perforation of the bowel before abdominal closure to minimise intra-abdominal infection. As a result, only six patients developed intra-abdominal or fungal infection.

Prophylactic antibiotic use, bowel preparation, selective bowel decontamination, and oral nystatin are designed to prevent post-operative infection. Contamination of the abdominal cavity is likely when a patient has had previous bilio-enteric anastomoses. Cultures of liver biopsy taken from the explant yield useful information and guide management in the early post-operative period. Twelve of the 27 episodes of infection were caused by multiresistant microbes including *Pseudomonas* spp. (n=6), methicillin-resistant *Staphylococcus aureus* (n=3), and *Candida* spp. (n=3) [Table 2]. Coliforms were found in seven episodes and were often mixed with these microbes. This finding is consistent with the selective effect of prophylactic antibiotics. The remaining episodes were related to viruses (n=6) and *Clostridium difficile* (n=1), which were obviously not susceptible to antibiotics or were a result of antibiotic treatment.

Table 2. Types of infection and responsible organisms in transplant recipients

Patient	Infection	Responsible organisms
1	Central catheter sepsis	Candida tropicalis
2	Intra-abdominal abscess and septicaemia (due to bowel perforation)	Klebsiella pneumoniae, Escherichia coli, (due to bowel perforation) Enterococcus faecium, Candida albicans, in both blood cultures, peritoneal fluid and necrotic tissues, Escherichia coli, Enterococcus faecium, Candida albicans
	Pneumonitis	Parainfluenza virus
3	Acute cholangitis (due to delayed biliary stricture)	Klebsiella spp., Pseudomonas aeruginosa, Enterococcus spp., Candida albicans
4	Pneumonitis	Cytomegalovirus
5	Urinary tract infection Groin wound infection	Enterococcus spp. Staphylococcus aureus (methicillin-resistant) Corynebacterium JK
6	Intra-abdominal abscess (due to bile leak)	Pseudomonas aeruginosa, Enterococcus spp.
	Central catheter sepsis	Morganella morganii
7	Lymphoproliferative disease	Epstein-Barr virus
8	Bronchopneumonia	Enterobacter spp., Klebsiella pneumoniae, Staphylococcus aureus
	Herpes zoster	Varicella-zoster virus
9	Central catheter sepsis Acute cholangitis (due to delayed biliary stricture)	Pseudomonas aeruginosa, Staphylococcus epidermidis Enterobacter cloacae, Klebsiella pneumoniae
10	Bronchopneumonia Urinary tract infection (due to colo-vesical fistula and acute diverticulitis)	Pseudomonas aeruginosa Escherichia coli, Staphylococcus aureus (methicillin-sensitive) Enterococcus spp., Escherichia coli
11	Pneumonitis Acute cholangitis (due to delayed biliary stricture) Pseudomembranous colitis	Cytomegalovirus Klebsiella pneumoniae Clostridium difficile
12	Hepatitis Pneumonitis Pseudomembranous colitis	Unknown viral agent Influenza A virus Clostridium difficile
13	Cytomegalovirus viraemia	Cytomegalovirus
14	Catheter sepsis	Pseudomonas paucimobilis
15	Chest infection Wound infection	Staphylococcus aureus (methicillin-resistant) Staphylococcus aureus (methicillin-resistant)
16	Infected intra-abdominal haematoma	Acinetobacter anitratus

Cytomegalovirus infection was the single most important infection after liver transplantation. Seronegative patients receiving CMV seropositive graft stood the greatest chance (60%) of developing a primary infection.[4] Primary infection can also occur (16%) in seronegative patients receiving seronegative graft.[6] The source of infection in the latter situation was from infected leucocytes in transfused blood. It is unfortunate that no proven strategy is available to prevent primary infection when the donor is seropositive and the recipient is seronegative.[4] When both donor and recipient are CMV seronegative, the use of CMV seronegative blood products or leucocyte filters are effective in preventing transfusion-related CMV infection. Fifteen per cent of CMV seropositive patients who receive a CMV seronegative graft may have a reactivation of the infection,[4] whereas when anti-lymphocyte globulin or OKT3 is used for treatment of rejection, the chance of this occurring is 45%.[7] A similar incidence (50%) of superinfection also occurs in CMV seropositive patients receiving CMV seropositive grafts. The infection in this case is of donor origin rather than endogenous origin. In CMV seropositive recipients, high-dose acyclovir administered for four months post-transplant can prevent CMV infection[8] but when such patients are treated for acute cellular rejection by steroid pulse, OKT3, or anti-lymphocyte globulin, ganciclovir at a dosage of 2 to 5 mg/kg/day for three months has been suggested to be useful.[7] However, the treatment time is inconvenient and the cost is prohibitive. Careful consideration of the benefit and risk ratio is necessary. In Hong Kong, the incidence of CMV seropositivity is high. The incidence of CMV infection in our series, however, was not alarming. This may be the result of the prophylactic measures adopted and the pre-emptive ganciclovir treatment given when surveillance for CMV yielded a positive result.

The risk of CMV infection is greater when a patient is immunosuppressed because of overdose of cyclosporin A or OKT3/anti-lymphocyte globulin treatment to counteract acute cellular rejection. Cyclosporine-based immunosuppression has been shown to result in more episodes of acute rejection than FK506 based-immunosuppression.[9] In the future, the use of FK506 as the primary therapy, or immediate shift to FK506 for cyclosporine-resistant rejection, rather than the use of OKT3 or antilymphocyte globulin will reduce the chance of CMV reactivation and possibly the occurrence of lymphoproliferative disorder.

Cirrhosis due to HBV is a common problem in Hong Kong. Patients with this diagnosis are not favourable transplant candidates because recurrence of the hepatitis is usually rapid after transplantation. As an immunomodulating virus, HBV increases the chance of infectious complications arising and increases the chance of mortality in the first six months.[10] Although prolonged administration of hepatitis B immune globulin can reduce the chance of recurrence, the cost is enormous.[2] Lamivudine is a useful drug to suppress viral replication.[3] Disappearance of HB_s was observed in one of our patients after transplantation and similar experience is emerging in other parts of the world. It is envisaged that a much greater proportion of hepatitis B patients will benefit from liver transplantation in the future.

The key factor in treating infectious complications in liver transplant patients is early detection and diagnosis. However, signs and symptoms are frequently inconspicuous. Prompt imaging studies, laboratory screening, and early laparotomy are important. Unexplained *Escherichia. coli* or *Candida* spp. septicaemia indicate contamination from the abdomen even though clinical signs may not be suggestive of bowel perforation. A CT scan may not be informative, as collections of bacteriae may be small and thin, but sufficient to produce septicaemia in an immuno-compromised patient. As long as the liver function is adequate, a re-laparotomy can be tolerated and surgical correction of the abnormality will lead to prompt recovery.

Infectious complications remain a major problem associated with liver transplantation. Given good care and adequate liver function, the majority of patients recover and lead a normal life. The development of complications, however, certainly prolongs hospital stay and increases the cost of treatment. To prevent these complications, the adoption of new immunosuppressive regimens that can prevent and treat acute rejection effectively, careful preservation of graft function, and meticulous surgical technique are key points that transplant surgeons and physicians should adhere to.

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