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Postoperative care of liver transplant patient

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Summary

The postoperative care of the liver transplant recipient is one of the most exciting challenges in clinical medicine. The complexity and diversity of complications are extraordinary. It is our hope that future liver transplant recipients will benefit from the sacrifices made by the many courageous individuals who have undergone this operation, providing us the experience needed to care for these critically ill patients.

Key words: *Liver transplantation, postoperative care, postoperative complications*

Introduction

With modern surgical technique very few liver transplant recipients die during surgery; nevertheless, 20-30 % of patients die within the first postoperative year. Of these deaths 75 % occur within the first two months following the operation [1]. Most liver transplant recipients have at least one significant postoperative complication. Differentiating and appropriately managing the diverse complications which can occur following liver transplantation is a formidable challenge. Thus, the postoperative care of liver transplant recipients warrants special emphasis [2].

Timing of complications

An understanding of the usual timing of particular complications can be quite helpful in generating appropriate differential diagnoses. Although there is some overlap, postoperative complications can be arbitrarily separated into four discrete periods: [1] immediate complications, which are seen within the first 48 hours of surgery; [2] early complications, which occur within the first month; [3] delayed complications, which occur from one to three months; and [4] late complications which are seen three months or more after transplantation.

I. Immediate complications

Primary graft non-function

Primary graft non-function is the most devastating complication which can occur following liver transplantation. This catastrophe, which usually results from hervesting or preservation injury to the donor liver, is heralded by sluggish bile flow, metabolic acidosis, progressive jaundice, severe coagulopathy, and renal failure in the immediate postoperative period. Retransplantation offers patients with primary graft non-function their only hope of survival; unfortunately, many patients die before a suitable donor liver can be obtained [3].

Post-operative hemorrhage

Intraabdominal bleeding is the most common cause of severe hypotension and renal failure in the first 48 hours following transplantation. Significant bleeding may be suspected by the presence of abdominal swelling, blood in abdominal drains, or hemodynamic instability. Tachycardia and hypotension associated with a fall in mixed venous 0_2 saturation and a significant decline in hemoglobin values indicate that the patient will in all likelihood require reoperation. If postoperative hemorrhage is recognized promptly, and if the patient can be stabilized with transfusions and returned quickly to the operating room, such bleeding is usually well tolerated. In contrast, a delay in diagnosis can result in irreversible hypotensive damage to the kidneys and liver.

II. Early complications

If the graft functions well and the immediate postoperative complications have been addressed successfully, the typical liver transplant patient enters a 5 to 10 day "honeymoon period" with few, if any, complications. However, from 7-21 days following transplantation, the patient enters a danger zone in which graft dysfunction is most likely to be seen. The most common causes of graft dysfunction include hepatic artery thrombosis, allograft rejection, biliary leak or obstruction, and infection. Accurate diagnosis and management of the various causes of graft dysfunction, whether intrahepatic or extrahepatic in origin, is one of the greatest challenges in the postoperative management of the liver transplant patient.

Hepatic artery thrombosis

Hepatic artery thrombosis is a common technical complication of liver transplantation, particularly in children, where it occurs in over 10 % of cases and often results in graft failure. Acute hepatic artery occlusion is a surgical emergency; if necrosis is allowed to progress before diagnosis and repair are carried out, the viability of the organ can be jeopardized and retransplantation then will be the only alternative.

Approximately one-third of patients with hepatic artery thrombosis develop fulminant hepatic necrosis within the first month after transplantation [4]. These patients have sudden, dramatic rises in serum transaminase levels associated with a progressive coagulopathy. Perhaps more common, and more difficult to diagnose, are lesser degrees of ischemic injury which result in focal areas of hepatic necrosis.

Hepatic artery thrombosis also may be the underlying cause of bile leaks within the first two mohths following transplantation. The blood supply to the transplanted common bile duct is critical to the integrity of the biliary anastomosis. Thrombosis of the hepatic artery can result in ischemia and partial or total disruption of the biliary anastomosis. Clinical features of a biliary leak, which can include bile peritonitis, subhepatic collections of bile, drainage of bile through abdominal drains, and bacteremia, should raise the possibility of arterial compromise.

Doppler ultrasound combined with real-time ultrasonography provides the best method of screening patients suspected of having hepatic artery thrombosis [5]. Ultrasonography can be done quickly and can be repeated as frequently as desired. If the hepatic artery cannot be identified by sonography, an arteriogram should be obtained. Conversely, if the hepatic artery is found to be patent, an arteriogram is not necessary and other etiologies for liver dysfunction should be sought.

Acute allograft rejection

Other than primary graft non-function and hepatic artery thrombosis, allograft rejection is the complication most feared by the transplant surgeon. Rejection of the serum bilirubin with little or no change in the transaminase and alkaline phosphatase values. Differentiating jaundice secondary to rejection from that due to biliary tract disorders, hepatic artery and portal vein thrombosis, systemic infection, and other forms of hepatocellular injury can occasionaly be quite difficult. The most accurate diagnostic approach includes cholangiography, duplex sonography, appropriate cultures, and liver biopsy. The biopsy can be helpful in excluding other forms of hepatocellular injury and often shows the typical histologic picture of rejection which uncludes periportal inflammation with mononuclear cells, bile duct destruction, invasion of the endothelium of the portal and central vein branches by mononuclear cells, and variable hepatocellular necrosis [6,7]. Overtreatment of suspected episodes or rejection exposes the patient to an increased risk of infection, often with fatal results. In contrast, excellent results have been achieved by limiting antirejection therapy to histologically confirmed episodes of rejection [8]. Serial biopsies, which can help define the course of patients undergoind treatment for rejection, can be safely performed either by creating a window over the liver for biopsy under direct vision or by using the standart

percutaneous approach.

Episodes of acute rejection often respond favorably to bolus injections of corticosteroids. Orthoclone OKT3 has been used successfully in treating steroid resistant cases [9]. If antirejection therapy is not successful within a short time, retransplantation should be considered.

Biliary tract complications

Complications of biliary tract reconstruction once were considered the Achilles heel of liver transplantation. Breakdown or obstruction of the biliary anastomosis occurred in a third of patients in the early experience at the University of Colorado and accounted for a 48 % mortality in the early experience at Cambridge University.

In adults, choledocho-choledochostomy now is the most commonly used reconstructive modality. When the common duct of the recipient cannot be used for reconstruction, as in children with biliary atresia and adults with sclerosing cholangitis, choledochojejunostomy to a Roux-en-Y limb is the usual approach. These anastomoses usually are stented with a T-tube for 4 to 6 weeks following surgery. Biliary complications are much easier to diagnose and manage in patients with these anastomoses and indwelling T tubes than in patients with cholecystojejunal anastomoses which provided limited acess to radiographic study. As a result, biliary tract complications are no longer major causes of postoperative morbidity and mortality following liver transplantation.

Bile leak can occur from one day to three weeks following transplantation. Suspicion of a biliary leak should be aroused either by the presence of bile in the intraabdominal drains or by a rise in the serum bilirubin level. Symptomatology depends on the timing of presentation and the degree of the leak. Leaks which are not localized usually cause bile peritonitis manifested by fever, abdominal pain, and a sustained and a steady rise in the bilirubin level with or without elevation of the alkaline phosphatase level. In contrast, a small leak can be asymptomatic if the bile is contained within fibrous reactions around the area of anastomosis. In these cases diagnosis can be accomplished only by routine T-tube cholangiography or by ultrasonography or computerized tomography.

Treatment should be tailored to the timing and degree of the leak. If the leak presents early and results in generalized bile spillage into the abdominal cavity or massive bile output through the drains, reexploration, resection and reanastomosis usually are necessary. However, in patients with well drained or contained small leaks, limited exploration and drainage usually results in satisfactory obliteration of the leak over a period of three to four weeks.

Biliary obstruction also is a common cause of postoperative jaundice following liver transplantation. Fortunately, strictures can be dilated using a variety of innovative and creative methods [10]. An unusual complication which occurred in a number of the early liver transplant recipients was the development of diffuse, amorphous "sludge" within the biliary tree. Careful flushing of the biliary tree during the donor harvest and improved methods of biliary reconstruction appear to have significantly decreased the incidence of this distressing problem. Sludge resulting from partial biliary obstruction often can be dissolved by continuous T tube irrigation of a heparinized saline solution.

Viral hepatitis

Although systemic infection may cause jaundice, the most common infectious cause of graft dysfunction is viral hepatitis. In the immediate postoperative period, the most common etiologic agents are the herpes viruses, including herpes simplex and cytomegalovirus, which are frequently seen following periods of aggressive immunosuppression. CMV hepatitis is usually a mild clinical illness. In contrast, hepatitis due to herpes simplex may result in fulminant hepatitis and loss of the graft. Diagnosis is made by finding characteristic pathologic changes in liver biopsy specimens as well as by detecting viral antigens and DNA by immunohistochemical stain-

ing techniques. Treatment consists primarily of reduction of the immunosuppression.

Non-specific postoperative jaundice

In addition to the fulminant form of harvesting-induced injury previously described, patients may suffer a more subtle form of procurement injury characterized by prolonged postoperative cholestasis, which can be misdiagnosed as rejection. Biopsies show marked cholestasis, particularly in central areas of the liver, as well as ductular proliferation and bile plugging, but without the inflammatory infiltrate characteristic of rejection [11]. These patients eventually recover with conservative management.

III. Deleyed complications

Delayed complications are seen most often in patients who have experienced a stormy postoperative course. Most important among these complications, each of which is associated with high mortality, are infection, renal failure, graft failure, and neurologic failure as well as a variety of iatrogenic disorders.

Infection

Infection is the leading cause of death in liver transplant recipients [12]. Preoperative infections requiring the use of antibiotics, the preoperative use of steroids and azathioprine, malnutrition, the invasive nature and extent of the operation, the catabolic postoperative state, the need for indwelling catheters and ventilators, and immunosuppression all expose the patient to an inordinate risk of infection with a wide variety of organisms.

Common bacterial infections following transplantation include sepsis, pneumonias, intraabdominal abscesses, and cholangitis. In the early experience with transplantation gramnegative enteric organisms and anerobes were frequently encountered particularly in association with biliary tract obstruction and infarction of the graft secondary to hepatic artery occlusion. Sepsis now is more often catheter related and, although some episodes are due to gram negative organisms, most are due to coagulase-negative staphylococci. The incidence of catheter sepsis for all types of critically ill patients is about 2 %; however, the incidence increases with the duration of catheterization.

Sytemic fungal infections, usually due to candidiasis and aspergillosis, are seen much more commonly in liver transplant recipients than in cardiac or renal transplant recipients. Over a third of patients may be affected [13]. Predisposing factors include the preoperative use of steroids and antibiotics, the duration of the transplant operation, the duration of subsequent operations, prolonged use of postoperative antibiotics, and treatment of rejection episodes.

The ominous prognosis associated with fungal infections is vividly illustrated by the fact that over two thirds of all patients with significant fungal infections following liver transplantation die, compared to a death rate of only 8 % in patients without fungal infections.

Important viral infections in liver transplant recipients include herpesvirus and cytomegalovirus infections. CMV can be cultured from the sputum and urine of most patients following liver transplantation; however, only a minority have sings of clinical infection [14]. CMV hepatitis is usually fairly well tolerated and responds to gentle reduction of immunosuppression. In contrast, CMV pneumonitis is often fatal. Herpes keratoconjunctivitis, stomatitis, and genital ulcerations are rarely serious infections, whereas pneumonitis is often fatal.

Renal failure

Renal failure is a common complication of liver transplantation. A number of factors can be implicated including: 1) preexisting renal insufficiency; 2) difficult surgery with associated hypotension; 3) poor liver function; 4) infection and the obligatory need for nephrotoxic antibiotics; and, 5) the use of Cyclosporin A [15].

Although great attention has been focused on the

nephrotoxicity of cyclosporine, rarely does cyclosporine cause severe acute renal failure in liver transplant recipients in the absence of other precipitating factors. The modest renal insufficiency which does occur with cyclosporine toxicity can usualy be managed by maintaining intravascular volume, lowering the dose of cyclosporine, and avoiding other nephrotoxic drugs such as amphotericin B, aminoglycosides, and trimethoprim.

A significant drop in urine output and increase in serum creatinine is commonly seen within the first week after liver transplantation; however it is uncommon for patient to require dialysis. The renal failure seen immediately following liver transplantation may be prevented by the prophylactic use of low dose dopamine during the operative and early postoperative period.

Much more ominous is acute renal failure associated with primary failure of the allograft, severe graft rejection, or overwhelming infection. Dialysis can alleviate fluid overload and electrolyte disturbances but has not been shown to improve survival in these desperately ill patients. Only correction of the primary process, usually by retransplantation, offers these patients any hope of prolonged survival.

Chronic allograft rejection

Approximately 10 % of liver transplant patients develop the "vanishing bile duct syndrome". This condition, which usually is preceded by an episode of acute allograft rejection, is progressive and irreversible necessitating retransplantation. The syndrome is characterized clinically by persistent cholestasis following an episode of acute rejection. Histologic features include disappearence of intralobular bile ducts as well as centrilobular necrosis and fibrosis [16]. The latter lesions are very suggestive of ischemic necrosis and are particularly intriguing since occlusion of medium sized arteries is seen in resected spesimens.

The pathogenesis of the vanishing bile duct syndome is not clearly defined. Some argue that the biliary ductular injury is not due to immunologic injury but results from ischemia secondary to severe arteritis and obliteration of medium sized hepatic arteries. The irreversibilitiy of the condition despite high dose immunosuppressive therapy has been used to support this hypothesis. Others argue that the condition is the result of cellular immunologic injury to both the biliary and vascular endothelium. This concept draws support from the fact that most, if not all, cases of the vanishing bile duct syndrome follow an episode of severe acute allograft rejection; moreover, the disappearance of bile ducts apparently can be reversed by aggressive immunosuppressive therapy of the acute rejection episode.

Neuropsychiatric complications

Among the most distressing complications which can occur following liver transplantation are neurologic disorders [17]. Air embolus and cerebral hemorrhage were seen early in the liver transplantation experience. These two disorders were eliminated by a carefully flushing the donor liver prior to revascularization and by meticulous postopirative control of coagulation parameters and hypertension.

Seizures and confusion are quite common within the first week following liver transplantation. Possible etiologic factors include toxic levels of cyclosporine, hypomagnesemia, hypocalcemia, and the use of certain antibiotics. In adtition, a few patients have developed pregressive quadriparesis and EEG changes suggesive of central pontine myelinolysis. Most disturbing are patients with prograssive seizures, profound metabolic encephalopathy, and renal failure requiring dialysis who ultimately die of multisystem disease. Autopsy in these patients reveals cerabral edema, swelling of astroctytes consistent with metabolic encephalopathy, and diffuse hypoxis neuronal damage. Although some episodes appear to be responsive to reductions in cyclosporine levels, this is not invariably the case.

Iatrogenic complications

Iatrogenic complications are not uncommon in these often critically ill patients. Particularly im-

portant among these are: (1) cardiac tamponade from erosion of central venous lines into the pericardium; (2) pneumothorax and hemothorax secondary to placement of central lines, liver biopsy, lung biopsy, and percutaneous cholangiography; and, (3) toxic epidermal necrolysis from antibiotics.

IV. Late Complications

Although most liver transplant recipients do extremely well after hospital discharge, they continue to be at risk for a variety of complications. Included among these are complications secondary to immunosuppressive therapy, recurrence of disease, delayed surgical complications, and complications of their preexisting disease, as well as an assortment of unusual miscellaneous conditions.

Complications of immunosuppressive therapy

The most common late complications experienced by liver transplant recipients are those related to the chronic administration of immunosuppressive agents. Of particular concern are the hypertension, renal insufficiency, and lymphoproliferative disorders associated with the use of cyclosporine A.

Hypertension

Hypertension is a common finding in liver, heart and kidney transplant recipients receiving cyclosporine A. The hypertension is characterized by elevation of peripheral vascular resistance and depression of the renin-angiotension-aldostoqerone axis (18). It is unclear whether the hypertension is due to a direct effect of cyclosporine A on the systemic vasculature or is secondary to acute or chronic renal injury; however, a number of laboratory studies suggest a role for renal vasoconstriction as a possible mechanism for the development of hypertension.

A variety of drugs have been used successfully in the treatment of cyclosporine-induced hypertension including nitroprusside, lopressor, captopril, niphedipine and diltiazem. Nitroprusside is the agent of choice in the immediate postoperative period because of the rapid reversibility of effect. In patients with persistent hypertension, lopressor, captopril, niphedipine or diltiazem can be used.

Renal failure

The pathogenesis of delayed renal failure in patients receiving cyclosporine is poorly defined (19). Cyclosporine administration results in a variety of hemodynamic alterations including a fall in effective renal plasma flow and glomerlar filtration rate. In addition, renal tubular dysfunction has been documented. Because renal biopsies show only mild to moderate changes, which correlate poorly with renal function, cyclosporine neprhotoxicity appears to be functional rather than structural in origin. However, despite the presumed functional nature of the condition, there is concern that the delayed renal insufficiency which appears months after transplantation may not be reversible with reduction or cessation of cyclosporine.

Lymphomas

Lymphoproliferative disorders are not uncommon in renal, heart, heart-lung, or liver transplant recipients receiving cyclosporine. These lymphomas, which typically involve the intestine and lymph nodes with sparing of the central nervous system, may occur within the first six months or as late as 2-3 years after liver transplantation. The majority of patients have been cured by drastic reduction or temporary cessation of immunosuppressive therapy (20).

Recurrent disease

Since most liver diseases are viral or immunologic in origin, recurrent disease is a potential risk for most, if not all, patients undergoing liver transplantation. However, in practice this has not been a common clinical problem. The two exceptions are in patients who undergo transplantation for hepatobiliary malignancies or for chronic hepatitis B infection.

Hepatobiliary malignancy

Liver transplantation for unresectable hepatic and biliary tumors is usually a futile endeavor. Recurrent disease, particularly in the liver and lung, occurs in the majority of patients within two years of transplantation [21]. In contrast, patients who are incidentally found to have a small hepatoma at the time of transplantation appear to have an excellent prognosis after transplantation. Although there are some anecdotal cases of long term tumor free survival for patients with tumors of the liver who are transplanted, the overall prognosis remains extremely poor. Even with extremely aggressive management including liver transplantation, high dose cyclophosphamide treatment, total body irradiation, and autologous bone marrow transplantation, metastatic disease recurrence is the rule.

Hepatitis B

With rare exception, all patients with hepatitis B have had recurrent infection of the allograft following liver transplantation despite the administration of massive doses of hepatitis B immune globulin [22]. In most patients recurrent hepatitis B virus infection is manifested by elevated transaminases and jaundice within the first six postoperative months. Differentiation of recurrent hepatitis B from allograft rejection usually requires one or more liver biopsies. Although most patients with hepatitis B become reinfected, their ultimate clinical outcome remains to be established. There is hope that, with careful modulation of immunosuppression, patients can function well for years after transplantation. It is equally unclear what the ultimate outcome will be for patients with delta hepatitis after liver transplantation. In one of the few reports available concerning the posttransplantation course of patients with delta hepatitis, 2 of 3 patients reacquired hepatitis B and delta hepatitis within the first three postoperative months.

Delayed surgical complications

Both portal vein and hepatic artery thrombosis can present late in the clinical course of a liver transplant patient, often with rather subtle clinical features. Recognition that the vascular supply to the liver may be compromised is important so that surgical repair can be performed appropriately.

Portal vein thrombosis

When portal vein thrombosis occurs, the presenting symptomatology depends greatly on the timing after transplantation. The closer the thrombotic event to the time of transplantation the more dramatic the biochemical abnormalities. If portal vein thrombosis occurs soon after transplantation, the clinical picture can resemble acute arterial thrombosis and can progress to hepatic necrosis. In contrast, when thrombosis occurs four to five weeks following transplantation, the biochemical abnormalities may be deceptively nonspecific. Of particular importance to the gastroenterolgist is variceal hemorrhage following liver transplantation, which should always raise the suspicion that portal vein thrombosis has occurred.

Suspected portal vein thrombosis should be confirmed by real time ultrasonography. If a patent portal vein cannot be demonstrated by these noninvasive means, arteriography should be performed. In those case where angiography is equivocal, transhepatic portal venography may be required to demonstrate occlusion of the portal vein.

Treatment of portal vein thrombosis consists of surgical exploration, declotting (by catheter embolectomy if necessary), and repair of the abnormality followed by either resection and reanastomosis or interposition graft.

Hepatic artery thrombosis

Relapsing bacteremia without an apparent source is the final, and most subtle, clinical presentation of hepatic artery thrombosis. In these patients, abnormalities of liver function may be deceptively mild; hepatic ischemia appears to be manifested in these patients primarily by decreased phagocytic capacity of the hepatic reticuloendothelial

system.

Complications of preexisting disease

Patients with primary biliary cirrhosis and sclerosing cholangititis may have complications associated with their underlying disease rather than the liver transplant, per se. Patients with primary biliary cirrhosis are at continued risk for pathologic fractures and vertebral collopse following liver transplantation, particularly within the first postoperative year; however, there are encouraging reports that enhanced bone formation begins to occur after this. Patients with long-standing ulcerative colitis who have undergone liver transplantation for sclerosing cholangitis remain at risk for the development of colon cancer. The optimum surveillance and management of these patients is unresolved.

Other unusual complications

Toxic shock syndrome, aplastic anemia associated with viral hepatitis, pneumococcal sepsis and the acquired immunodeficiency syndrome have been reported following liver transplantation. Two cases of toxic shock syndrome associated with staphylococcal infections have been observed. In addition, fatal cases of aplastic anemia in children after transplantation for fulminant non-A, non-B hepatitis have been reported. Patients who undergo splenectomy at the time of transplantation are at risk for the development of overwhelming pnoumococcal sepsis. Finally, given the large number of blood transfusions administered at the time of transplantation, it is not surprising that patients may become infected with the human immunodeficiency virus with its attendant morbidity and mortality.

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Letter to the editor

To the editor of Paediatrik Cerrahi Dergisi
Re: the letter to the editor from dr Şeref Etker published in your journal vol 3 (1) 1989

First I want to thank dr Etker for his interest and comments on my review on postnatal physiological function adaption in newborn infants. In our own studies and those quoted the measurements have been performed in premature babies and full-term infants to estimate physiological capacity of various renal function and their postnatal changes. It was not intended to be a comprehensive text-book chapter on all possible pathophysiological conditions. These were only hinted at in the review article. However recently published new studies on renal function and fluid therapy in high risk infants (ref I) and controversies in fluid and electrolyte therapy for the premature infants (ref II) do support the conclusion of my review: very low-birthweight infants and infants with respiratory distress syndrome and perinatal asphyxia constitute a group of highrisk infants who may have abnormal renal functions. This abnormality should be recognized and anticipated in order to provide appropriate fluid therapy to avoid undesirable clinical morbidities and complications. Still agree with dr Etker that appropriate fluid therapy varies with the individual patient and the disease state. Therefore fluid management in the nursery must include the pathophysiological losses that too require replacement therapy. I also agree with the point that several factors affect maintenance homeostasis during transition to extrauterine life besides the changing renal function, for instance the changing bodywater composition and environmental factors related to insensible losses through skin and respiratory tract in addition to the special conditions of neonatal paediatric surgery cases. I also agree with dr Etkers last comment regarding the fact that many problems attributed to immatury may often be consequenses of environmental or iatrogenic distress.

Sincerely yours
Nils Svenningsen, M.D., Ph.D.

Ref I: Oh, W: Renal function and fluid therapy in highrisk infants. Biology of the neonate, 1988, vol 53:230-236.
Ref II: Costarino AT, Baumgart S: Controversies in fluid and electrolyte therapy for a premature infant. Clinics in perinatalogy, 1988, 15:863-878.