Chapter 38

Postoperative Care Following Hepatic Transplantation

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The perioperative care of liver transplant recipients challenges even the most skilled intensivists, anesthesiologists and surgeons. Few other patient populations routinely manifest as many synergistic problems and conflicting needs. Because multisystem failure is a relatively frequent catastrophe in liver recipients, the intensivist caring for these patients must be knowledgeable in many subspecialties, and have day-and-night availability of experienced consultants. Particularly invaluable are consultants with expertise in infectious diseases, radiology and pathology [4,37].

The rate of postoperative complications generally reflects not only the skill of the transplant team, but also the quality of the donor organ and the illness severity of the recipient. To a certain extent, a patient who is stronger and healthier at the time of surgery can be expected to manifest a more rapid and less complicated recovery. Outcomes will be better than average when relatively narrow selection criteria for both the recipient and the donor organ are adopted. The converse is also true, i.e., transplant centers which accept critically ill patients and transplant marginal organs will experience higher risks of morbidity and mortality. Thus, it is difficult to compare centers or interpret outcome statistics unless the previous factors are comparable (Table 38.1).

The intensivist who cares for transplant recipients postoperatively must be familiar with the surgical procedure [15,20], and should observe several operations from start to finish. After induction of general anesthesia, and placement of venous, arterial, pulmonary artery and bladder catheters, surgery begins. When veno-venous bypass is to be used, outflow cannulas are inserted into the portal vein and one femoral vein, and an inflow cannula is placed in the ipsilateral axillary vein. Bypass flow begins when the catheters are unclamped and both the supra- and infrahepatic portions of the vena cava are cross-clamped. The devascularized liver is excised and removed. After the orthograft liver is positioned in the hepatic bed, the vena cavae and portal veins are anastomosed. When these vessels are unclamped, the donor liver is perfused by the recipient's circulation. At the moment of unclamping and reperfusion the risk of acute hyperkalemia (released by liver effluent) and cardiovascular collapse is highest. Then bypass cannulas are clamped and removed. After the hepatic artery anastomosis is completed, attention is turned to surgical hemostasis. Either the bile duct is sutured end-to-end with the recipient's duct and a T-tube brought externally for drainage, or a choledochojejunostomy Roux-en-Y anastomosis is created and bile drains internally. After a cholangiogram demonstrates proper channelling of bile, the incision is closed; the patient is then transferred to the ICU.

These patients usually arrive in a transitional hemodynamic state: operative blood loss has ceased; high rates of operative fluid administration have been tapered, while extracellular fluid shifting continues; inhalational anesthetics (both vasodilatory and cardiodepressant) are being eliminated; operating room hypothermia is being reversed. The donor liver begins compensating for its predecessor's functional inadequacy.

In transferring the patient to the care of the intensivist, the anesthesiologist should convey all information about the patient's physiology and operative course which may affect subsequent management. Usually this includes

J. Tinker et al. (eds.), *Care of the Critically Ill Patient*

Table 38.1. Profile of the adult liver transplant patient population at the University of Pittsburgh 1987–1990

Preoperative diagnosis (%)		
Biliary cirrhosis		*12*
Alcoholic cirrhosis		*12*
Chronic active hepatitis B		*21*
Chronic active hepatitis non A–non B		*11*
Sclerosizing cholangitis		*8*
Retransplantation		*16*
rejection		*5*
primary non-function		*6*
other retransplantation		*5*
Other		
Number of cases		*1751*
Female		47%
Male		53%
	Mean	Range
Age (years)	44	14–75
Intraoperative course		
Operative time (min)	718	303–1560
Blood administered (units)	10	0–185
Vasoactive drug infusions		26%
Treated for fibrinolysis		17%

preoperative mental status and activity level, intraoperative hemodynamics (including baseline levels of cardiac output, optimal right- and left-heart filling pressures); a recent hematocrit, pH and potassium level; urine output rate and response to diuretics; gas exchange and other indices of pulmonary function; the use of, or any adverse reactions to inotropic or vasopressor agents; quantity of fluids and blood products administered; estimation of the adequacy of clotting at the end of the operation; dosage of long- or short-acting anesthetics, sedatives or muscle relaxants; occurrence of untoward events, and implications of their management. (For example, the use of long-acting benzodiazopines to produce amnesia during stormy intraoperative episodes can contribute to slow reawakening and must be included in the differential diagnosis of postoperative coma; long-acting muscle relaxants can act for days in the patient with impaired renal function and may hamper efforts to wean and extubate the patient.)

Postoperative orders follow the standard format for critically ill surgical patients. Sedatives and narcotics are not routinely ordered, but are administered as needed to avoid inadvertent oversedation. Short-acting opioids (e.g. fentanyl) are preferable to benzodiazepines and antihistamines for simple pain management. Physical therapy is begun early to maintain flexibility and to prevent injury (e.g. foot-drop from prolonged plantar flexion in comatose patients).

The patient remains in the ICU until he/she no longer requires ventilatory support or airway maintenance, is hemodynamically stable without continuous infusions of vasoactive drugs, and has either stable or improving liver function.

These complicated patients need well-organized care. One tool useful for sorting out and tracking ongoing problems is a bedside flow chart. This flow chart can be a wall poster with dated grid spaces for recording information on critical reference values: vital signs, doses of immunosuppressive agents, antibiotics and blood products administered, diagnostic invasive and non-invasive procedures, weight, fluid balance, culture reports and laboratory results. Ready access to such information is valuable for the numerous consultants and nurses involved, who must otherwise queue up for the patient's chart. An organized and prominently displayed bedside flow chart facilitates timely and informed decision-making.

The importance of coordinating the patient's care cannot be overemphasized. To avoid multiple or conflicting approaches to problems, important management decisions should be channelled through one physician responsible for implementing and coordinating care. This physician performs a complete physical examination of the patient daily, reviews any orders, periodically reviews the overall care plan and medication records, obtains study reports and communicates with consultants and family. A fragmented approach to patient care is inefficient and can be dangerous.

Immunosuppression

Cyclosporine has dramatically improved survival following transplantation [13,14]. This drug, a lipophilic cyclic polypeptide derived from fungal metabolism, suppresses the immune response by inhibiting T cell-mediated production of Interleukin-2, a lymphokine which promotes clone expansion of antigen-stimulated T lymphocytes [1,29]. It also appears to spare T suppressor-cell function, thus enhancing natural immunosuppression.

Cyclosporine is highly bound to plasma proteins, red blood cells and lipoproteins. GI tract absorption is erratic and incomplete.

Cyclosporine is metabolized in the liver by cytochrome P450 mixed function oxidases; its half-life is shortened by drugs which induce hepatic metabolism (e.g., barbiturates, phenytoin). Conversely, ketoconazole, whicn inhibits hepatic metabolism, will prolong the drug's half-life and raise serum levels. Renal clearance is minimal (approximately 1 ml/min) and cyclosporine is resistant to both hemo- and peritoneal dialysis [33].

Cyclosporine dosage varies from center to center, depending upon whether other immunosuppressants are used and the precise plasma level sought, usually 200–1000 ng/ml. Generally the parenteral dose ranges from 1 to 5 mg/kg per day and is given in two or three equally spaced doses. Serum trough levels are drawn just prior to a subsequent dose. Oral administration of cyclosporine, begun after postoperative ileus resolves, requires a much larger dose, 10–15 mg/kg per day.

Importantly, cyclosporine can be quite nephrotoxic [9,34], and the nephrotoxic effects of concurrently administered aminoglycosides, furosemide (frusemide) or amphotericin B are additive and possibly synergistic. Decreases of glomerular filtration rate, likely due to reversible renal vasoconstriction, appear dose-related. Distal tubular injury, manifested by impaired sodium reabsorption and free water clearance, may occur. Magnesium wasting, another sign of cyclosporine's tubular injury, often leads to a reduced seizure threshold.

Mild degrees of cyclosporine-induced hepatotoxicity can be camouflaged in liver transplant recipients. Renal transplant patients receiving cyclosporine show a 30%–50% incidence of direct hyperbilirubinemia [1]; elevations of alkaline phosphatase and the transaminases occur as well. Distinguishing this dose-dependent cholestatic syndrome from rejection of the liver allograft or biliary obstruction can be difficult. Liver biopsy usually reveals a benign histologic pattern.

Cyclosporine-induced neurotoxicity may manifest with a large number of signs and symptoms [3]. Most common are tremulousness, paresthesias, confusion, seizures, psychosis and coma. Cortical blindness, quadriplegia, cerebellar ataxia, headache, flushing and tetany have been described. These dramatic side effects generally subside as cyclosporine levels fall. Hypomagnesemia presents an additional risk factor for cyclosporine neurotoxicity [30]; less well appreciated is the role of hypocholesterolemia [3].

Because non-cardiogenic pulmonary edema has been attributed to bolus administration of cyclosporine through a central venous catheter [24], slow infusion (over one hour) is recommended. Peripheral infusions are avoided because of the high incidence of venous thrombosis.

Steroids (e.g., 1 g of methylprednisolone), are first given at the time of revascularization of the new liver and are tapered over 10 days to replacement doses. Acute episodes of rejection are treated with another 7–10 day course of high-dose steroids. Insulin-resistant hyperglycemia, metabolic alkalosis, and psychosis are the most frequent clinical problems associated with steroid therapy in the recipient.

Azathiaprine is given in many liver transplant centers, at a dose of 25 to 50 mg/day; myelosuppression is the major complication of its use [22].

When an additional immunosuppressant is required, murine monoclonal anti-human T cell antibody (OKT3) is administered. It can be used either to treat acute rejection unresponsive to high-dose steroids, to allow lower doses of cyclosporine in patients with impaired renal function, or to treat prophylactically the recipient of an ABO-incompatible liver [7,28,36]. The first doses of OKT3, a protein of murine origin, may precipitate dramatic, life-threatening reactions: anaphylaxis, bronchospasm, pulmonary edema, seizures, fever, chest pain, nausea, aseptic meningitis, hypotension or serum sickness. Our current practice includes premedicating the patient with high-dose steroids and antihistamines; the dose of OKT3 is given by a physician, and vital signs are carefully monitored for several hours. Resuscitation equipment and drugs should be available.

Patients receiving OKT3 are followed with blood T3 (CD3) lymphocyte counts (levels less than 50 cells per mm^3 are sought). Serum OKT3 levels can be measured, as can serum anti-OKT3 or anti-murine antibodies. Anti-murine antibodies in titers greater than 1:100 are associated with a poor clinical response to subsequent doses of OKT3.

FK506, another interleukin-2 inhibitor, is currently undergoing clinical trials in hepatic transplant patients [28,29].

Function of the Transplanted Liver

After a liver has been grafted, evidence of its function can be observed during the later stages of the operation: bile drains from the open end of the donor bile duct, coagulation improves without administration of clotting factors, fibrinolysis resolves, and elevated serum lactate levels decline.

Postoperatively, liver enzymes and function tests are checked at least daily and close attention is paid to abnormal values. Initially, serum prothrombin time and bilirubin are lower than preoperative values, due to intraoperative administration of clotting factors and washout of bilirubin during hemorrhage and blood replacement. In the postoperative period, even small increases in either of these parameters are worrisome and prompt further scrutiny. When available, bile should be examined. In the patient with a biliary duct-to-duct anastomosis and external drainage of bile via a T-tube, bile output can be quantified and inspected. Healthy bile resembles used motor oil; pathologic bile may be thin, green or yellow, or of small quantity.

Primary Non-Function of the Transplant

Early plasma transaminase elevations can represent ischemic harvest injury, and these values should return to normal by the fifth postoperative day. Poor hemodynamic management of the donor, with prolonged hypoxemia, hypotension or cardiac arrest prior to organ harvesting, can result in ischemic insult and impaired function of the grafted liver. Then prothrombin time and bilirubin levels increase, and the transaminase levels may reach several thousand units. Although function of a severely injured liver may gradually improve, often it must be quickly replaced, before secondary complications intervene [27].

Harvest injury associated with plasma transaminase elevations greater than 3000 iu has a dismal prognosis. In these cases, the liver is irreversibly injured by ischemia, thrombosis of a portal vessel, or unknown mechanisms. Such injured livers, termed "primary non-function" organs, subsequently undergo massive necrosis, and must be replaced immediately. Primary non-function resembles fulminant hepatic failure with worsening coagulopathy, renal failure, ARDS, hypoglycemia, cerebral edema, hypotension, acid–base disorders, and hyperkalemia causing death. During emergency retransplantation, these patients usually demonstrate dramatic improvement when the necrotic liver is excised. So desperate is this situation that one transplant center has reported performing temporizing hepatectomies while seeking new donor organs [26].

Treatable Causes of Graft Dysfunction

Postoperatively, when previously improving liver function suddenly deteriorates, investigation should first be directed to common and treatable causes of graft dysfunction: rejection, hepatic artery thrombosis and extrahepatic biliary obstruction. Experience shows that these three complications have similar liver function profiles. Failure to include each possiblility in the differential diagnosis can be dangerous [6,16].

Rejection

Rejection during the first few postoperative days is unusual. Hyperacute rejection, if it occurs, is extremely rare. Accelerated cell-mediated rejection can occur after 48 to 72 hours. Rejection typically begins 10 to 14 days after surgery, presenting with fever, right upper quadrant tenderness, and elevation of plasma bilirubin, alkaline phosphatase, transaminases, and prothrombin time. Percutaneous liver biopsy, after correcting an elevated prothrombin time to less than twice normal, is the appropriate diagnostic procedure. Liver biopsy is never a benign procedure, and the patient must be watched closely for evidence of intra-abdominal bleeding. Routine liver biopsy is not recommended, but should be reserved for patients with deteriorating hepatic function. Based upon a clinical decision, immunosuppression may be boosted pending biopsy results.

Graft-Versus-Host Reaction

Currently, donors and recipients are usually of similar ABO blood type. In urgent circum-

stances [10], e.g., fulminant hepatic failure, a compatible but non-identical donor organ is transplanted, i.e., O liver into an A, B, or AB recipient, or either an A or B liver into an AB recipient. In such cases, the patient may undergo a graft-versus-host reaction, typically commencing from 10 to 21 days after surgery. Hemolysis, thrombocytopenia and leukopenia are prominent features, but fever, reticulocytosis and hyperbilirubinemia can occur. Usually mild and self-limited, hemolysis can be severe, with associated DIC, acute tubular necrosis, and shock.

Management of this reaction includes replacement transfusion with washed red cells of the donor type, and maintaining a high renal tubular flow rate to "flush out" toxic pigments. Plasmapheresis is sometimes used in an attempt to rid the patient of antibodies. When an incompatible donor organ is transplanted, usually in emergency situations, hemolysis is the major complication.

Surgical Complications [16,19]

Hepatic Artery Thrombosis

This is usually a devastating event in the adult recipient, heralded by the rapid onset of septic shock. Elevations of plasma transaminases are generally more dramatic than increases in bilirubin or prothrombin time. Diagnosis is made by ultrasound (lack of pulsatile flow), with confirmation by hepatic arteriography. Hepatic artery thrombosis is usually an indication for retransplantation in the adult, although reports of survival after emergency hepatic artery reconstruction have been reported [32].

Though its presentation is usually dramatic, hepatic artery thrombosis can present as relapsing bacteremia. Since the arterial supply to the donor bile duct stems from the thrombosed hepatic artery, bile duct necrosis and biliary sepsis may follow. Finding either bile or biliary pathogens in abdominal drainage suggests a bile leak. *Candida* cultured from abdominal drains, in the absence of systemic candidiasis, suggests bile leakage, and necessitates evaluation of both the hepatic artery and the bile duct for repair or reconstruction.

Whenever the diagnosis of hepatic artery thrombosis is made, the patient's bile (if drained through a T-tube) should be cultured, and biliary pathogens (*Klebsiella, E. coli*, enterococcus) treated prophylactically. This should be undertaken while the patient is prepared for either hepatic artery reconstruction or retransplantation. Hepatic artery thrombosis can result in hepatic gangrene, another indication for urgent retransplantation (though the usual outcome is death).

Anecdotes occasionally suggest that overzealous clotting factor replacement may cause hepatic artery thrombosis, but the issue is controversial. Multifactorial analysis failed to support this impression, and only showed a positive correlation with hematocrit above 44% [31].

Extrahepatic Biliary Obstruction

This can be caused by an obstructed T-tube or by stenosis of the bile duct [27], either at a suture line or elsewhere. Obstruction usually presents as acute cholangitis with fevers and increased bilirubin and transaminases. Either T-tube cholangiography, percutaneous transhepatic cholangiography or endoscopic retrograde pancreaticocholangiography is undertaken to diagnose the site of obstruction. Biliary reconstruction must be undertaken if the degree of obstruction is significant.

Post-transplant portal vein thrombosis can occur in patients who previously had low portal vein flow, either from preoperative portal vein thrombosis, phlebitis or portosystemic shunts. Fortunately this catastrophic event, leading to sepsis and fulminant hepatic failure, is rare [16].

Other Causes of Graft Dysfunction

Viral infections may cause an acute deterioration of liver function. Patients who were hepatitis B antigen-positive prior to transplantation will invariably reinfect the donor liver [5]. Cytomegalovirus (cmv), Epstein-Barr, delta agent and adenovirus are other sources of viral hepatitis. Often immunosuppression must be decreased until improvement occurs. The risk of acute rejection is lessened during viral infection because infection weakens the immune system.

Pancreatitis can lead to worsening liver function. Slight or moderate increases of serum amylase are frequently observed in the early postoperative period, and probably reflect operative manipulation of the pancreas. Usually the patient is asymptomatic, and the serum amylase rapidly returns to normal. The pancreas can be significantly injured when either

a portal vein graft or a hepatic arterial conduit is tunnelled beneath it during transplantation [16]. In such patients, amylase elevations are higher and more prolonged. Treatment is conservative, and patients are periodically scanned to detect pancreatic pseudocyst formation. Outcome is usually good. However, hemorrhagic or necrotizing pancreatitis associated with acute hepatitis B reinfection or reactivation is most often fatal.

Medical Complications

Infection

Infection is a common and devastating complication of transplantation. Given the high incidence of nosocomial infections, a meticulous approach to infection control must be practised. Gloves must be worn while touching the patient or attached catheters, ostomy appliances or airway equipment. Care must be exercised to avoid allowing sleeves or neckties to spread infection.

Debilitated or neutropenic patients, who may also be given steroids, may not readily develop fevers when infected. If a fever occurs, an extensive examination to determine the source may be necessary. After a thorough physical, including inspection of all wounds, vascular catheters in place more than three days are changed and cultured. Cultures are obtained of blood, urine, and sputum, drains, tubes and wounds. A chest X-ray and abdominal films are taken. Non-invasive procedures, such as computerized tomography of the abdomen, ultrasound examination of the portal region, and radiologic examination of the sinuses are obtained when appropriate. Invasive procedures such as closed-catheter bronchoscopic sputum retrieval, bronchoalveolar lavage, spinal tap, liver biopsy and paracentesis may also be indicated. Examinations for *Legionella*, Epstein-Barr virus and CMV should be pursued.

Non-infectious causes of fever should also be considered: rejection, drug (especially OKT3) or transfusion reaction, hepatic artery thrombosis, phlebitis, hematoma and pulmonary embolism. Nonetheless, untreated infections can be so catastrophic that one is hard-pressed to justify any delay in instituting antibiotic coverage while awaiting culture results.

Wound infections are quite common, prolonged operative duration in a crowded operating room adding an important risk factor. Coagulation defects cause wounds to ooze, providing a hospitable milieu for pathogens. Abdominal wounds are easily inoculated by contaminated ascites drained at the start of the operation, or during the biliary reconstruction, either from an open bile duct or bowel. Groin and axillary incisions can be enveloped by intertriginous skin folds where heat and moisture promote superficial infection. It is imperative that all wounds be inspected daily.

If positive blood cultures in the donor are reported, the recipient should be treated promptly for the same pathogen. When bacteremia recurs in a patient receiving antibiotics, the search for a closed-space infection (e.g. sinus, subhepatic space, obstructed biliary system), where pathogens are protected from antibiotic penetration, should be undertaken. Relapsing bacteremia may be a presenting sign of hepatic artery thrombosis.

In a comprehensive review of 101 consecutive liver transplant recipients, Kusne and coworkers analyzed the sources and types of infection, associated risk factors, and outcomes [17]. This report is highly recommended to physicians involved in post-transplant care. They found that 83% of the patients became infected, and 67% developed severe infection. A correlation between infection and mortality was measured: 23 of 26 patients who died (88%) had severe infection at the time of death. Most of these deaths occurred during the first two months after transplantation.

Bacteremia occurred in 26% of the patients, with a 50% mortality. The following sources of bacteremia were identified: intra-abdominal (33%), urinary tract (21%), line sepsis (6%), and pneumonia (6%). Pathogens isolated were Gram-negative aerobes (51%), Gram-positive aerobes (27%), anaerobes (9%) or polymicrobial (12%).

Bacterial pneumonia developed in 14% of patients (with a nearly 50% mortality). Half of these cases represented nosocomial infections of intubated patients. Intra-abdominal or liver abscesses developed in 13 of 101 patients, with 38% dying.

Cytomegalovirus infection was frequent (22%), but usually not diagnosed until 16 days after surgery. Neutropenia and atypical lymphocytosis were the most frequent signs. Disseminated CMV infection with pneumonia was invariably fatal. CMV gastroenteritis, while not

necessarily fatal, had significant morbidity associated with profuse GI bleeding. DHPG (9-[1,3 dihydroxy-2-propoxymethyl] guanine, an acyclic nucleoside analogue) is currently recommended for treatment of CMV infections.

Invasive candidiasis occurred in 13% of patients, with a high mortality. Esophagus, bladder, and intra-abdominal abscesses were common sites of infection, but this pathogen may be isolated from blood and peritoneal fluid as well. Amphotericin B remains the treatment.

Pneumocystis carinii pneumonia was diagnosed in 11% of postoperative patients, but usually not until the third week after surgery. Fever, cough and dyspnea were the usual symptoms. Radiographic infiltrates were either localized or diffuse. Trimethoprim-sulfamethoxazole is the initial treatment, pentamidine being added or substituted if pneumonia fails to improve. When patients with pneumocystis pneumonia became superinfected with CMV, the outcome was invariably fatal.

Analysis of preoperative risk factors yielded a positive association between severe postoperative infections and either an elevated serum alanine aminotransferase (ALT) or a decreased T cell helper/suppressor ratio. Transplant operations lasting longer than 12 hours and intraoperative transfusion of more than 25 units of blood or 30 units of plasma were also major risk factors. Surprisingly, neither the steroid dose, cyclosporine levels nor use of azathioprine was associated with an increased risk of infection. Interestingly, OKT3 recipients were found only to have an increased number of protozoal infections.

Pulmonary Complications

After infection, pulmonary complications are the second most common non-surgical cause of postoperative morbidity. This is hardly surprising when chronically ill patients, malnourished and weak, undergo long operations, with bilateral subcostal incisions, and major fluid and blood replacement. Postoperative respiratory function can be further compromised by pleural effusions (100% incidence of right-sided effusions, 30% left-sided) [21], atelectasis, or reaccumulation of ascites, with impaired diaphragmatic excursion. When the mobilization of fluids sequestered in tissues is superimposed upon acute renal insufficiency, volume overload can become a difficult problem. Low oncotic and high hydrostatic pressures lead to increased lung water and decreased lung compliance, thereby increasing the work of breathing in patients with minimal respiratory reserve.

Pneumonias are common in hepatic recipients, with a 15% bacterial, 11% pneumocystis and 5% CMV incidence. Lung abscesses and empyemas also occur but less commonly. Intermittent segmental or lobar atelectasis is observed in 25% of all liver transplant recipients. Contributing factors include diaphragmatic and phrenic nerve injury from vena cava clamping, difficulty in clearing secretions, and pleural effusions. Management may require bronchoscopic suctioning of mucus plugs, drainage of pleural effusions via small indwelling pig-tail catheters, and application of PEEP. To expand lung volume, the patient lies with the atelectatic lung segment in a non-dependent position, inhales while positive inspiratory pressure is applied and held at approximately 40 cm H_2O for several seconds, then exhales. This sequence is repeated several times, whereupon the patient is returned to mechanical ventilation. Such a maneuver can be dangerous in hypovolemic or hypotensive patients and the arterial pressure tracing must be watched closely.

Airway management is guided by conservative application of standard principles. Extubation is deferred until patients are adequately oxygenated with less than 50% inspired oxygen concentrations and 5 cm H_2O PEEP, normocarbic with minute ventilation less than 130% normal, hemodynamically stable, strong enough to cough secretions, and able to protect their airways, i.e. completely awake and alert. Because of the potentially catastrophic consequences of aspiration by immunosuppressed patients, extubation is postponed if there remains any doubt about the patient's mentation level, or the function of the grafted liver. A significant decline in liver function, regardless of the etiology, can cause rapid development of encephalopathy and impaired airway protection. Either normal or improving liver function is an additional criterion for extubation. The value of early tracheostomy in these patients is unproven.

CNS Complications

Typically, dramatic improvement of mental status occurs during the first 24 h after hepatic transplantation, with steady gains over the next

several days. Persistent obtundation must be aggressively investigated so that reversible metabolic (cyclosporine toxicity, hyper- or hypoglycemia, hypothyroid or uremic encephalopathy) and surgically treatable (subdural hemorrhage) causes can be corrected before irreversible injury occurs. Other sources of altered mentation, including an ICU psychosis, depression, CMV infection and depressant drug effects of clonidine, OKT3, H_2 blockers, sedatives, hypnotics and narcotics should be considered as well.

Patients with fulminant hepatic failure, whether from viral infection, Wilson's disease, trauma, or acute, overwhelming graft rejection, often develop severe cerebral edema. In such cases, maneuvers which decrease intracranial pressure, including blood pressure control, water and salt restriction, diuresis, mannitol administration and hyperventilation, should be undertaken. Intracranial pressure monitoring may be of value, though the additional risk of infection and bleeding must be taken into account.

Seizures are not uncommon, with an incidence of 10% after hepatic transplantation [35]. The most likely causes are cyclosporine toxicity (usually with associated hypomagnesemia) and intracranial hemorrhage. Although anticonvulsant therapy is not often required, such drugs (e.g., barbiturates, phenytoin) may increase cyclosporine metabolism by the liver. Therefore, cyclosporine levels must be evaluated when anticonvulsants are administered.

Cardiovascular Complications

Patients undergoing hepatic transplantation usually have excellent myocardial function. Cardiac output is frequently two to three times normal, compensating for increased arteriovenous shunting. Since O_2 consumption is not significantly altered, mixed venous O_2 saturations are increased, typically to 85%–90%. After transplantation, these parameters are little changed; however within several months the cardiac output, systemic vascular resistance and mixed venous O_2 saturation return to more normal values.

In the immediate postoperative period, blood pressure usually reflects an intravascular volume which becomes progressively smaller as oozing, third space losses and rewarming occur. When these processes subside, hypertension invariably develops as a side effect of cyclosporine therapy. The resultant risk of catastrophic intracranial bleeding in patients with a residual coagulopathy mandates control of hypertension. Parenteral antihypertensives such as labetalol and hydralazine are usually effective and it is unusual for infusions of nitrates to be required. Methyldopa is avoided because of its hepatotoxicity.

Dysrhythmias are uncommon and usually reflect electrolyte (especially potassium and magnesium) derangements. Myocardial infarction is uncommon despite an often stormy intraoperative course with prolonged periods of tachycardia and hypotension.

Renal Function

Following infection and respiratory complications, renal impairment is the third common postoperative medical problem. Patients with chronic liver disease often have pre-existing renal insufficiency. Fulminant hepatic failure is frequently accompanied by acute renal failure (hepatorenal syndrome). Preoperative renal failure is a certain indicator of increased postoperative mortality [2]. During hepatic transplantation, the kidneys can be injured by a hypotensive episode, high renal vein pressure (inferior vena cava clamping without venous bypass), massive transfusion of blood products, or the rapid parenteral administration of cyclosporine, a potent nephrotoxin.

Estimating the precise extent of renal impairment can be difficult. Due to a reduced muscle mass, the "normal" creatinine level of the cirrhotic patient is well below normal; small increases in serum creatinine can indicate far larger decrements of renal function. Single creatinine values will not represent steady state levels. Plasma urea nitrogen values are similarly imprecise: either disproportionately high due to postoperative hematoma resorption or abnormally low from malnutrition. Calculation of the creatinine clearance is probably the best means of estimating renal function.

Studies of large numbers of patients place the incidence of preoperative renal dysfunction near 25%, rising to as high as 67% postoperatively [25]. Successful efforts to decrease the incidence of renal failure after transplantation include infusing dopamine (1–2 μg/kg per min) from the start of surgery until 48 h postoperatively [23]. In some liver transplant centers, the initial administration of parenteral cyclosporine to patients with acute renal impair-

ment is postponed until renal function improves following transplantation [8].

Managing the liver transplant recipient with renal failure is difficult. Balancing an adequate right-heart filling pressure against the risk of hepatic venous congestion is often problematic. Inadvertent volume overload is difficult to correct, since many of these patients are resistant to loop diuretics. Both ethacrynic acid and bumetanide can be effective when used with furosemide. Continuous venous hemoultrafiltration can be added to manage diuretic-resistant volume overload and tissue edema, which impair the patient's respiratory function and overall mobility. When hemodialysis is required, close attention must be directed to residual anticoagulation by heparin.

Nutrition

Chronically ill patients who require liver transplantation are often severely malnourished [12]. Their muscle mass is greatly decreased, and protein is sequestered in ascites. While many of these patients would probably benefit from preoperative nutritional support, a precise risk to benefit ratio has not been defined. Postoperative weaning from mechanical ventilatory support is sometimes difficult due to lack of strength. Our usual practice is to begin parenteral alimentation on the day following surgery. Patients are then given a total of 30 kcal/kg daily, composed of 0.5 to 1.0 g/kg protein, up to 7 g/kg carbohydrate and 6 kcal/kg fat. Lipid emulsions are necessary to balance the caloric intake, but the danger of giving lipids to patients with severe lung injury is uncertain [11]. Large steroid doses given in the early postoperative period often result in some degree of insulin-resistant hyperglycemia, necessitating continuous insulin infusion. Enteral alimentation is instituted when bowel peristalsis returns.

Postoperative Bleeding

Experience teaches transplant surgeons that meticulous surgical hemostasis is vital. Commonly, an hour or more of operative time is devoted to securing hemostasis, since unless the surgical field is quite dry prior to closure, the patient will likely require re-exploration for continued bleeding. During the first few days after transplantation, drainage from the Jackson-Pratt abdominal drains is quantified frequently. Large volumes of bloody drainage might be due either to hemorrhage or to rapid reaccumulation of ascites. The hematocrit of drainage fluid often helps to determine its nature.

When intra-abdominal bleeding occurs, attention is focused upon refilling intravascular volume and correcting coagulation abnormalities. Maintaining a hematocrit of 30%, a platelet count over 50 000/mm^3 and clotting times less than 50% above control are reasonable goals. If, after correction of any coagulopathy, intra-abdominal bleeding is greater than one blood volume over 24 hours or one liter per hour, the patient is taken to the operating room for re-exploration.

It is imperative that intravascular volume deficits be corrected before inducing general anesthesia. Therapeutic endpoints include maintaining a stable central venous and pulmonary artery wedge pressure, and a urine output greater than 0.5 ml/kg per h in patients with good renal function. When available, mixed venous O_2 saturation is a most useful indicator of adequate O_2 delivery to tissues, since the level is extremely sensitive to changes of both cardiac output and O_2 carrying capacity.

When large volumes of citrated blood products are infused, hypocalcemia, due to citrate intoxication, must be corrected to avoid myocardial depression and loss of vascular tone. It is important, therefore, to measure serum ionized calcium levels and to replace calcium deficits.

Correction of defective coagulation can be guided by thromboelastography [15], which provides a qualitative analysis of clot formation thus aiding selective replacement therapy. In vitro addition of either protamine or epsilon aminocaproic acid to the patient's blood will demonstrate those coagulation disorders (residual heparin effect or fibrinolysis) which can be corrected by these agents.

A source of GI tract bleeding is often difficult to pinpoint. Possible sites include esophageal varices, stress- or steroid-induced gastric ulcers, diffuse hemorrhage from CMV enteritis, rectal hemorrhoids, or arterial bleeding at the gastrojejunostomy anastomosis.

Intra-abdominal infection may cause explosive and irreparable bleeding when vascular anastomoses or mycotic aneurysms rupture. Chronic steroid treatment further weakens tissue structure and can make surgical repair impossible.

Massive transfusion appears to be a more difficult undertaking when performed outside the operating room. Large bore IV catheters, pressurized warming devices, and trained personnel are extremely useful in this endeavor. The reader may wish to consult his anesthesia colleagues for additional technical advice.

Outcomes

The hepatic transplant recipient who is not greatly debilitated at the time of surgery, and who is fortunate enough to avoid severe infection, renal failure or a recurrence of hepatic malignancy, has the best chance of survival. Of the 25% of all patients who die during the first year after liver transplant, most will die during the first 60 days [2,13,14] of either infection or renal failure. Later deaths (after hospital discharge) are most often from rejection or malignancy.

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