

Intensive care management of liver transplanted patients

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Abstract

Advances in pre-transplant treatment of cirrhosis-related organ dysfunction, intraoperative patient management, and improvements in the treatment of rejection and infections have made human liver transplantation an effective and valuable option for patients with end stage liver disease. However, many important factors, related both to an increasing "marginality" of the implanted graft and unexpected perioperative complications still make immediate post-operative care challenging and the early outcome unpredictable. In recent years sicker patients with multiple comorbidities and organ dysfunction have been undergoing Liver transplantation; appropriate critical care management is required to support prompt graft recovery and prevent systemic complications. Early post-operative management is highly demanding as significant changes may occur in both the allograft and the "distant" organs. A functioning transplanted liver is almost always associated with organ system recovery, resulting in a new life for the patient. However, in the unfortunate event of graft dysfunction, the unavoidable development of multi-organ failure will require an enhanced level of critical care support and a prolonged ICU stay. Strict monitoring and sustainment of cardiorespiratory function, frequent assessment of graft performance, timely recognition of unexpected complications and the institution of prophylactic measures to prevent extrahepatic organ system dysfunction are mandatory

in the immediate post-operative period. A reduced rate of complications and satisfactory outcomes have been obtained from multidisciplinary, collaborative efforts, skillful vigilance, and a thorough knowledge of pathophysiological characteristics of the transplanted liver.

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Key words: Post-liver transplant critical care; Liver transplantation; Post-operative complications; Liver graft dysfunction

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INTRODUCTION

Liver transplantation (OLTx) has become a widely accepted treatment for a variety of liver diseases, such as viral and alcoholic cirrhosis, liver malignancy, acute liver failure, and many metabolic abnormalities. As a result of improvement in anesthesiological and surgical skill, organ support device adoption, advanced understanding of transplant immunology, and better critical care management of complications, liver transplanted patients survive longer. However, several major challenges such as the use of marginal donors and impaired recovery of the graft, along with a number of post-operative adverse events may negatively affect the evolution of the procedure, resulting in a limited success on an individual basis.

As patients with multiple comorbidities and organ dysfunction are undergoing OLTx, an appropriate critical care management is required to support prompt graft reco-

very and prevent systemic complications.

The early post-operative period is a crucial time when strict monitoring and sustainment of cardiorespiratory function, frequent assessment of allograft performance, timely recognition of unexpected complications and prompt treatment of extrahepatic organ system dysfunction are mandatory. Intensive care management of liver transplanted patients mainly centers on rapid hemodynamic stabilization, correction of coagulopathy, early weaning from mechanical ventilation, proper fluid administration, kidney function preservation, graft rejection prevention, and infection prophylaxis.

POST-OPERATIVE CIRCULATORY INSTABILITY, HEMODYNAMIC MONITORING AND STABILIZATION

Besides relying on intrinsic hepatic cell recovery, maintenance of post-operative graft function also depends on optimization of liver hemodynamics and prevention of venous stasis. Subclinical hypovolemia, or excessive cardiac filling resulting in pulmonary edema and deterioration of gas exchange, may lead to inadequate graft perfusion and increase post-operative morbidity. Patients with cirrhosis tend to have impaired ventricular contractility in response to physiologic stress or pharmacologic stimulation. Additionally, metabolic disturbances, in the form of acidosis, hypothermia, and electrolyte disturbance can further reduce cardiac performance and lead to circulatory instability. Hemodynamic depression may also be a long-term result of the reperfusion syndrome and/or a consequence of hypocalcemia-induced citrate intoxication from massive transfusion. Other causes of post-operative hypotension are a pre-existing dilated cardiomyopathy, the potential for coronary artery disease, and an unrecognized hypovolemia from various factors, including hemorrhage, third space losses, and ongoing ascites formation. The possibility of perioperative myocardial infarction causing left ventricular dysfunction must be kept in mind in cases of refractory circulatory dysfunction. Post-operative “subclinical” pulmonary edema is not infrequent, with at least 50% of these episodes developing within the first 24 h. The rapid improvement of systemic vasodilatation, which can result in a sudden increase in the afterload, is another potential cause of excessive strain on the heart. Because of potential cardiocirculatory instability and the need to optimize cardiac output and organ perfusion, hemodynamic monitoring must be strictly carried out in the immediate post-operative period. Knowledge of the preload and afterload indexes of both right (RV) and left ventricle (LV), mean and transpulmonary pressure, and pulmonary vascular resistance (PVR), is useful in managing pharmacologic interventions, volume therapy, and vasoactive drug administration. A pulmonary artery catheter (PAC) equipped with a fast response thermistor capable of assessing RV ejection fraction (RVEF%) and ventricular filling through RV end diastolic volume calculation (RVEDV), and/or the PiCCO System (Pulsion Medical

System, Munich, Germany) are regularly used in many institutions. The application of the transpulmonary thermodilution single indicator technique (PiCCO System) allows the determination of continuous cardiac output, based on the pulse contour method, along with estimation of preload index (intrathoracic blood volume, ITBVI) and “lung edema” index (extravascular lung water, EVLWI)^[1]. Indicator dilution-derived ITBVI has been considered a sensitive indicator of cardiac preload because volume changes preferentially alter the volume in the intrathoracic compartment, which serves as the primary reservoir for the left ventricle^[2]. The Stroke volume variation (SVV) and pulse pressure variation (PPV) are also continuously obtained with the transpulmonary thermodilution single indicator technique, and are considered the best parameters (dynamic parameters) in predicting fluid responsiveness in mechanically ventilated patients after various surgical procedures^[3]. Hemodynamic optimization following OLTx aims at preventing inadequate cardiac filling, which results in suboptimal tissue perfusion and “distant” organ failure. Continuous monitoring of dynamic parameters of fluid responsiveness and/or assessing RV end diastolic filling and RVEF% are helpful in maintaining an adequate central blood volume. Optimizing cardiac output will avoid excessive fluid administration, thus preventing both pulmonary congestion and an unrecognized increase in the sinusoidal and hepatic vein pressures. In liver transplanted patients a vasodilated and hyperdynamic state may take days or weeks to regress to near normal levels. Moderate filling followed by vasoconstriction should effectively treat this evolving clinical condition. If hypovolemia needs to be corrected, synthetic colloids have proven to be as successful as albumin solutions^[4]. Failure to increase systemic vascular resistance or reduce the level of vasoactive support indicates a poorly functioning graft. Dopamine or dobutamine are generally administered to increase the inotropic function whereas vasoconstriction can be achieved with low dose noradrenalin or terlipressin.

Fluid and electrolyte management

Intraoperative hypovolemia and significant blood loss usually require massive amounts of intravenous fluid and blood products to preserve cardiac output and organ perfusion. However, massive blood transfusion with fluid administration is not free from complications in the post-operative period. Levy *et al*^[5] demonstrated with a large population of liver transplanted patients that one of the significant predictors of readmission to the ICU was the amount of blood product administered intraoperatively. Generous fluid replacement may result in volume overload, water-sodium retention, a capillary leak syndrome in the third space, and may further aggravate graft congestion and edema caused by ischemia-reperfusion syndrome. Once post-operative hemodynamics have been stabilized, it is necessary to promote the return of the sequestered fluid from the peripheral circulation and third space back to the central circulation. An appropriate negative fluid balance in the first day after operation apparently decreases the incidence of early pulmonary complications and may

be associated with improved oxygen delivery to the graft^[6]. Lowering right ventricular volume and pressure would create a venous pressure gradient between the portal and central venous circulation that draws blood through the donor graft.

A rational approach to maintaining circulating volume is by providing two-thirds of required fluids with crystalloid and replacing half of drain losses with 5% albumin. The real advantage of albumin solutions on the final outcome is still under debate as the evidence for a specific benefit has been substantial only in the setting of decompensated cirrhosis^[7]. A few reports have addressed the benefit of using albumin after OLTx. While a judicious use of human albumin solution, coupled with fluids low in sodium has the potential to restore oncotic pressure, promote intravascular mobilization of fluid and prevent an excessive increase in plasmatic sodium^[8], in the study by Mukhtar *et al*^[9], post-operative albumin administration targeted to “normalize” the serum level did not improve the immediate outcome. Cohen *et al*^[10] found no correlation between the relatively low serum albumin level on admission to the ICU and the incidence of post-operative complications. Although the post-operative transfusion policies may differ among centers, the replacement of blood components to achieve hemoglobin between 8 and 10 g/L, as commonly adopted during transplant surgery, could be a valid approach^[11]. Maintaining a post-operative hematocrit between 25 and 30% would be helpful to guarantee an adequate oxygen delivery to the new graft. Post-operative electrolyte imbalances are related to the pre-transplant nutritional status, intraoperative events, fluid shifts, and citrated banked blood. Common disturbances include hypokalemia, hyperkalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypoglycemia, hyperglycemia, and hypomagnesemia. Hyperkalemia is observed in the post-operative period secondary to albumin washout of the preservative fluid and to the kidney's reduced ability to regulate potassium levels. It can be worsened by immunosuppressors. Normal glucose metabolism is a sign of a well-functioning allograft. Hypoglycemia can be an ominous sign of compromised liver recovery. Hyperglycemia on the other hand is very common, as a consequence of steroids, calcineurin inhibitors, surgical stress, and diabetes mellitus.

POST-OPERATIVE VENTILATORY SUPPORT AND WEANING FROM MECHANICAL VENTILATION

The intraoperative use of short-acting anesthetics and neuromuscular blocking agents in many cases allows a prompt recovery of consciousness and neuromuscular tone, which are essential for a rapid discontinuation of ventilator assistance. In some patients tracheal extubation is feasible immediately at the end of the surgical procedure, whereas others are stabilized in the ICU before discontinuing ventilation in order to ensure that liver

function is satisfactory. Various clinical results suggest that an early or very early tracheal extubation (immediately in the operating room or within 3 h post-operatively) has been associated with a persistent maintenance of satisfactory gas exchange. The incidence of reintubation was not increased thereafter when compared to patients extubated later^[12,13].

Mandell *et al*^[14] demonstrated that their protocol for early extubation and rapid transfer of liver recipients from the ICU to the surgical ward did not negatively impact on long-term outcome, as 1- and 3 year graft and patient survival were above the national average. Besides increasing the risk of ventilator-associated pneumonia^[15], prolonged mechanical ventilation can worsen venous congestion of the liver graft. Ventilation-induced increased intrathoracic pressure may, in fact, reduce venous return from the inferior vena cava and hepatic veins^[16]. However, in cases of serious preoperative encephalopathy, marked hypoxemia, severe obesity, important hemodynamic disturbance, primary graft dysfunction, and pulmonary edema, an immediate tracheal extubation is neither feasible nor recommended. Post-operative ventilatory failure from unsuccessful early extubation may be associated with impaired oxygen delivery to the newly grafted liver. Although successful in many patients, optimal selection criteria and timing for early extubation are not yet well defined by the current literature. Furthermore, it may not be possible to generalize results from the centres who recommend this strategy due to differences in preoperative clinical conditions, surgical skill and post-operative staffing resources. A difficult weaning from mechanical ventilation is very often a consequence of post-operative respiratory complications, which can be attributed to massive transfusion, pleural effusion, inadequate clearance of bronchial secretions, pneumonia, and adverse effects of immunosuppressive therapy. Acute respiratory distress syndrome (ARDS) is one of the prominent complications following OLTx. Its main causes include a severe reperfusion syndrome, substantial blood loss, prolonged operation and early post-operative infections. The pathophysiologic mechanisms of transfusion-related acute lung injury (TRALI), a causative factor of ARDS, seem to be related to donor alloantibodies that react against granulocytes or leucocyte antigens (anti-HLA)^[17]. The management and treatment of respiratory complications, including ARDS, are primarily supportive, with obligatory mechanical assistance in cases of ventilatory failure. Sometimes these patients prove difficult to wean due to unsatisfactory gas exchange during various T-piece trials. In these circumstances a rapid extubation followed by an immediate application of a non-invasive ventilatory support should be considered in order to shorten and accelerate the weaning process. Non-invasive ventilation (NIV) by adding a pressure support (PS) with a continuous positive end expiratory pressure (PEEP), could prevent the loss of vital capacity and impede severe lung derecruitment following extubation. As opposed to the first applications in solid organ transplantation when NIV was mainly delivered by full facial mask^[18], nowadays it is predominantly delivered by the helmet system.

Daily experience shows that the helmet is suitable for long application of NIV. Improvements in manufacturing have led to a reduction in air leaks while guaranteeing a satisfactory delivery of high inflation pressures. The first application of NIV in solid organ transplant recipients was described by Antonelli *et al.*^[18]. They randomized patients with respiratory failure following transplantation to receive either NIV or standard therapy. Patients assigned to NIV showed a trend toward less ventilator associated pneumonia and a significant reduction of severe sepsis or septic shock episodes. If post-operative respiratory failure is severe enough to require a prolonging of mechanical ventilation, ventilatory strategies that minimize insults to both the lung and the allograft should be used. Airway pressures and PEEP should be set in order to improve oxygenation without simultaneously impairing liver outflow. In liver recipients affected by severe ARDS, low tidal volume (6 mL/kg of ideal body weight), relatively high respiratory rates and PEEP confer a survival advantage by keeping the lung open and avoiding atelectasis and shear stresses on lung units^[19]. Mechanical ventilation with high PEEP has been reported to impair liver outflow. Besides determining an increased retrograde blood accumulation and liver edema, an excessive PEEP (> 10 cm/H20) may also depress the splanchnic perfusion and hepatic performance by increasing venous stasis in the portocaval system and depressing cardiac output^[20]. However, Saner *et al.*^[21] demonstrated in 74 hemodynamically stable liver transplant recipients that flow velocities of the right hepatic vein, portal vein, and hepatic artery were not decreased by PEEP up to 15 cm H20. When critical hypoxemia occurs in the setting of a severe respiratory failure inhaled nitric oxide may be administered. High frequency oscillation and the prone positioning have been utilized with some positive results but have not yet been studied extensively.

ASSESSMENT OF GRAFT FUNCTION

Liver graft recovery mainly depends on pre-transplant clinical conditions, donor quality, perioperative stable hemodynamics, sufficient organ blood flow, and prevention of venous stasis on the graft. Donor-related factors (e.g. hepatic steatosis), use of vasoactive drugs, hemodynamic changes, surgical-related aspects along with vascular and biliary complications may lead to a highly variable performance of the allograft. Continuous monitoring of the post-transplant graft function is required to identify subtle, early findings of graft dysfunction which require aggressive management aimed at prevention of graft failure. Unfortunately, on-line monitoring of liver function at the bedside is not available. Traditionally, assessment of liver function is based on static and dynamic tests. Static tests include serum dosage of liver enzymes and bilirubin along with the monitoring of protein synthesis, mainly albumin and coagulation factors. Liver transaminases may be markedly elevated in the post-operative phase but gradually decrease over the course of several days. Enzyme levels may reflect the extent of hepatocellular necrosis (high activities of alanine

aminotransferase-ALT are present in the periportal region of the liver) or cholestasis (e.g. alkaline phosphatase, or γ -glutamyl transferase). Hepatic protein synthesis is easily assessed by monitoring of factor V (half-life 4 h) and VII (half-life 5h). The dynamic tests express the ability of the liver to metabolize or eliminate defined substances. The ability to convert lidocaine to monoethylglycinoxylidide metabolite (MEGX test) was used to evaluate both the hepatic metabolic capacity and liver blood flow^[22]. The indocyanine green (ICG) clearance test is routinely used in some centers to quantify the functional activity of the graft in relatively short time intervals. After intravenous injection, ICG is almost exclusively eliminated by the liver into the bile and does not undergo enterohepatic recirculation. ICG removal from the blood depends on liver blood flow, parenchymal cellular function and biliary excretion. ICG elimination may be expressed as half-life time, blood clearance, or plasma disappearance rate (ICG-PDR). An ICG-PDR under 15%/min is associated with a higher rate of primary dysfunction. However, ICG-PDR is not exclusively a marker of cell function but also of blood flow to the liver and short-term variations in ICG-PDR probably reflect changes in blood flow rather than hepatocellular function^[23].

IMMUNOSUPPRESSION

In-depth discussion of the pharmacology of immunosuppressive medications is beyond the scope of this article, although certain issues are worth mentioning. There have been many recent advances in immunosuppressive drugs, but the most common protocols continue to consist of the calcineurin inhibitors associated with steroids. Cyclosporine achieves its effects through reversible inhibition of immunocompetent lymphocytes in the G0 and G1 phases of cell division. T-helper cells are the primary targets of the drug, although T-suppressor cells may be affected. Cyclosporine also works by inhibiting calcineurin and thereby impairing interleukin 2 (IL-2) transduction. Tacrolimus, like cyclosporine, suppresses humoral immunity through inhibition of B-lymphocyte activation. Tacrolimus also inhibits calcineurin which, in turn, results in decreased IL-2 production and dampening of T-cell recruitment and activation. In general, tacrolimus and cyclosporine are fairly similar in terms of graft and patient survival. However, O'Grady *et al.*^[24] and Kelly *et al.*^[25] demonstrated that the incidence of acute and steroid-resistant rejection was significantly lower with tacrolimus than with cyclosporine treatment. Mycophenolate mofetil has been used for years as an adjuvant immunosuppressive agent. It works by selectively inhibiting purine synthesis, and thus is a potent inhibitor of B-cell and T-cell proliferation. Mycophenolate's major role at present is in treating acute rejection although drug is gaining an increasing role in maintenance immunosuppression. It is renal sparing and does not necessarily require drug monitoring. Corticosteroids are used routinely as part of the maintenance protocol for solid organ transplant recipients, and are the most important

Table 1 Side effects and toxicity of the commonly used immunosuppressive agents

Agent	Side Effect/Toxicity	Agent	Side Effect/Toxicity
Cyclosporine A	Hypertension Neurotoxicity (tremor, paresthesias, Headache, confusion, seizures) Nephrotoxicity Hepatotoxicity Hyperkalemia/Hypomagnesemia Gastric atony, nausea, vomiting Gingival hyperplasia, hypertrichosis	Antilymphocyte globulin	Leukopenia/Thrombocytopenia Systemic symptoms
Tacrolimus (FK 506)	Hypertension, dyspnea, palpitations Headache, tremor, paresthesias, seizures, focal neurological deficits Nephrotoxicity, hyperkalemia Glucose intolerance, nausea, vomiting thrombocytopenia	OKT3	Non-cardiogenic pulmonary edema Encephalopathy/Aseptic meningitis Systemic symptoms
Glucocorticoids	Hypertension/Fluid retention Psychosis, mood changes Glucose intolerance Adrenal suppression Electrolyte abnormalities Peptic ulcerations, pancreatitis Osteoporosis, myopathy, aseptic necrosis	Mycophenolate mofetil (MMF)	Hypertension Hyperkalemia/Hypophosphatemia Anemia Arrhythmias (tachycardia) Muscle weakness
Sirolimus	Bone marrow suppression (thrombocytopenia, anemia, leukopenia), hyperlipidemia, peripheral edema, and poor wound healing	IL-2R basiliximab [simulect], daclizumab [zenapax]	Rashes, fever, and gastrointestinal symptoms

agents in the management of acute rejection. Sirolimus is a macrocyclic triene antibiotic which prevents T-cell proliferation by inhibiting IL-2 transduction and inducing the cell to arrest at the G1 to S phase of the cell cycle. It is increasingly being used as both primary and rescue immunosuppression, and has the advantage of being both renal sparing and reducing the need for high-dose steroids. Induction therapy, while not frequently used after OLTx, may be an effective approach. The newer IL-2 receptor-blocking antibody preparations, daclizumab (Zenapax) and basiliximab (Simulect) are common drugs for induction immunosuppression^[26]. The most significant adverse effects and toxicity of the commonly used immunosuppressors are reported in Table 1. Nowadays intense investigations are directed at adopting renal sparing protocols, reducing the dose or eliminating calcineurin inhibitors, switching patients with renal dysfunction to sirolimus, and attempting abstinence from corticosteroid because of their well known side-effects^[27].

INFECTION PROPHYLAXIS

Infections remain problematic following OLTx, and are still the primary causes of death. Prolonged hospital stay before the transplant and the immunocompromised status predispose the recipient to colonization with resistant micro-organisms. Due to heavy immunosuppression the early post-operative period poses greater risks of infection. The source of the infecting organisms can be: a) the

donor organ and transfused blood products b) the reactivation of previous infection c) invasion by exogenous micro-organisms or by endogenous flora.

Wound infections, pneumonia, peritonitis, cholangitis, urinary and catheter-related infections, *Clostridium difficile* colitis, and liver abscesses are similar to the hospital-acquired infections observed in other surgical patients^[28]. Coagulase-negative and coagulase-positive *Staphylococci*, *Enterococci*, anaerobes, and Gram-negative bacteria such as *Escherichia coli*, *Enterobacter* species, and *Pseudomonas aeruginosa* are common in surgical-site infections. Pneumonia after OLTx is usually caused by Gram-negative bacilli, *Enterobacter* species, *Serratia marcescens* and methicillin-susceptible or methicillin-resistant *Staphylococcus aureus*. *Enterococci* are frequent pathogens, and infections with vancomycin-resistant *Enterococci* (VRE) have become a troublesome complication^[29]. Risk factors for VRE bacteremia include Roux-en-Y choledochojejunostomy, biliary strictures, prolonged ICU stay, and CMV infection. Treatment of bacterial infections generally involves characterization of the infective agent (e.g. cultures and antibiotic sensitivities), source control (e.g. catheter removal and debridement), and antibiotic regimens based on the hospital antimicrobial susceptibility patterns. Immunosuppression must be reduced or even halted temporarily. Prophylactic post-operative antibiotics are primarily tailored to gram negative (*Pseudomonas sp*, *Enterobacter sp.* and *Klebsiella sp*) and gram-positive organisms (*Staphylococcus aureus*). Viral infections account for substantial morbidity and mortality following

OLTx. Human herpes virus 1 (herpes simplex virus) reactivation is a common viral illness and requires a 10- to 14-day course of acyclovir (5-10 mg/kg q8h). CMV status (positive or negative) of the donor must be recorded in the recipient's chart, and the CMV antibodies of the recipient must be checked in order to ascertain the need for prophylaxis. CMV infection can affect the capacity of the host to mount a defense against complicating infections. Patients with systemic CMV infections are treated with ganciclovir. The drug appears to be most effective when started early in the course of CMV infection, and may be useful for CMV hepatitis, enteritis, and pneumonia. Fungal infections usually develop as a consequence of depressed host defenses and environmental exposure. The risk of fungal infections increases when acute rejection episodes are treated with high dose of corticosteroids or antilymphocyte agents. Predisposing factors for fungal infections include preoperative renal dysfunction, fungal colonization at baseline, severity of end stage cirrhosis, retransplantation, perioperative massive transfusion, need for extracorporeal renal assistance, prolonged ICU stay, Human Herpes Virus-6, and reintubation. Both *Aspergillus* and *Candida* species can be found after OLTx. As a general rule, if *Candida* species grow from two or more sites, even if not from blood (eg, urine, wound), the condition should be managed as a systemic infection. The presence of *Candida* species in peritoneal fluid strongly suggests a bile leak or bowel perforation. Although antifungal prophylaxis has been widely studied, no consensus exists on which patients should receive it. The presence of the above risk factors likely indicates the need for antifungal prophylaxis. Many centers target prophylaxis mostly toward *Candida* spp. with fluconazole, 400 mg daily. Low-doses of a lipid formulation of amphotericin B (1-3 mg/kg per day) or echinocandins are also recommended. Echinocandins are preferred in many institutions due to their lack of significant drug interaction with the immunosuppressive agents and the favorable safety profile. If *Aspergillus* is a target pathogen, based on local epidemiology, either caspofungin or lipid formulations of amphotericin B should be used for prophylaxis. Caspofungin, 70 mg load on day 1 followed by 50 mg/d has been associated with a successful treatment outcome^[30]. Serious infectious diseases complicating the post-transplant course are associated with poor graft recovery, prolonged stay in the intensive care unit (ICU), and a high risk of multi-organ failure. Septic shock early after OLTx is difficult to manage since it is almost always unresponsive to conventional "aggressive" therapy. As underlined in the Surviving Sepsis Campaign Guidelines^[31] multiple associated interventions have proven beneficial in improving the outcome of severe infections. Adjuvant therapies, such as IgM-enriched intravenous immunoglobulins (Pentaglobin[®]), have been recommended in association with full combination treatment to sustain the failing organs in cases of severe sepsis.

The administration of recombinant human activated protein C (drotrecogin alfa, Xigris[®], Eli Lilly Indianapolis Ind), an anti-inflammatory and antithrombotic drug, has also been proposed for management of life-threatening

sepsis in liver transplant patients^[32].

The measurement of procalcitonin may add some useful clinical information on potential ongoing bacterial infection. Zazula *et al*^[33] demonstrated that procalcitonin levels increase transiently for about 24 h after OLTx and thereafter rapidly decrease if no bacterial infection is present. However, the variations of procalcitonin level are highly dependent on the type of immunomodulatory therapy the patient is receiving. Polyclonal antithymocyte globulin (ATG) administration was, in fact, associated with an increase in serum procalcitonin even in the absence of any evidence of infection. According to the authors, measurements of procalcitonin may lead to conflicting interpretation in some circumstances as some immunosuppressors or adjuvants may be a significant stimulus for the synthesis of this biomarker.

POST-OLTx NUTRITION THERAPY

Patients with end-stage liver disease frequently have abnormalities of carbohydrate, lipid, and protein metabolism. Concentrations of plasma aromatic amino acids (AAA: phenylalanine, tyrosine, tryptophan) as well as methionine increase, while plasma branched-chain amino acid levels (BCAA: valine, leucine, isoleucine) decrease. Preoperative malnutrition has been associated with an increased risk of post-operative infections, respiratory complications and a prolonged stay in the ICU^[34]. Factors such as stress from surgery, the release of catabolic hormones, and corticosteroid administration, enhance the need for nutritional support after transplantation.

Energy requirements are only moderately elevated in the early period of uncomplicated OLTx. For this reason, some authors recommend that the caloric intake, determined by using the formulation provided by the Harris-Benedict equation, should be provided at approximately 120%-130% of the calculated basal energy expenditure (BEE)^[35]. As nitrogen loss is raised as a consequence of increased protein catabolism, liver transplant patients during the acute post-transplant phase should receive 1.5 to 2.0 g of protein per kilogram of dry weight^[35]. The potential persistence of post-operative encephalopathy does not require a reduction of protein content in the diet but only a change of amino acid composition in favour of BCCA-enriched formulae^[36]. Early post-operative nasoenteric tube feeding is preferred over total parenteral nutrition (TPN) unless a patient has a nonfunctional gastrointestinal tract or requires complete bowel rest. Although gastric and colonic ileus may be present following transplantation, early enteral nutrition is usually tolerated^[37]. Tube feeding results in decreased metabolic response to stress, fewer technical and metabolic problems, and enhanced visceral protein synthesis^[38]. Hasse *et al*^[39] demonstrated that early enteral feeding prior to oral diet initiation was associated with significantly greater cumulative 12-day calorie and protein intakes than controls. In addition, results showed decreased rates of viral and bacterial infections and fewer infected patients in the tube-fed group than in the control

Table 2 Early post-operative complications following OLTx

Graft dysfunction	Rejection	Vascular thrombosis
Primary nonfunction	Hyperacute	Hepatic artery thrombosis
Preservation injury	Acute	Portal vein thrombosis
Small for size syndrome		
Neurologic complications	Biliary complications	Electrolyte disturbances
Encephalopathy	Stricture	Hyponatremia
Seizure	Leaks	Hypocalcemia
Coma	Obstruction	Hyperkalemia
Psychosis	Dilation	Hypokalemia
Aphasia		Hypophosphatemia
Tremors		Hypoglycemia
Anoxic-ischemic events		Hyperglycemia
Central pontine myelinolysis		Hypomagnesium
Gastrointestinal	Drug interactions	Pneumonia
Ileus	Interference with CYP3A4	Renal dysfunction
Ulcer		Atelectasis
Bleeding		Infections
Diarrhea		Bleeding and coagulopathy

OLTx: liver transplantation.

group.

Patients should be encouraged to start oral diets as soon as feasible although tube feeding should not be discontinued until patients are able to maintain an oral intake adequate to their nutrition requirements (at least 80% of normal nutritional need). Electrolyte disturbances in the acute post-transplant period should be monitored closely and properly replaced if needed.

EARLY POST-OPERATIVE COMPLICATIONS

Despite substantial technological, medical and surgical advances, OLTx remains a complex procedure that is accompanied by significant morbidity. Frequent complications on both the graft and the organ systems arise because of multiple, and sometimes unavoidable adverse events. The most common complications of the early post-operative course are briefly described in the following paragraphs, and some others are outlined in Table 2.

Primary graft failure

Primary graft failure is characterized by the incapacity of the new graft to maintain the recipient metabolic homeostasis, and is associated with a high risk of death without an emergency retransplantation. The incidence of primary failure ranges between 2-14%^[40]. Beyond a series of predisposing conditions such as donors' advanced age,

hemodynamic instability, prolonged ischemia time, severe reperfusion damage, the exact causes are undetermined. The patient exhibits signs of severe graft dysfunction including significant CNS changes, coma, serious coagulopathy, oliguria, jaundice, and hypoglycemia. Liver transaminases are often greater than 5000 U/L, Factor V < 10%, and prothrombin time < 20%. Treatment includes avoiding the administration of potassium, transfusing fresh frozen plasma every 4-6 h or as needed, and keeping the gastric pH greater than 5.0. A continuous 10% dextrose solution infusion may be needed to control hypoglycemia. Center-specific reports of supportive therapy utilizing prostaglandin E1, N-acetylcysteine, plasmapheresis, and liver assisting devices have been described, but with no confirmed positive results on a large scale^[41]. If no recovery of graft function occurs within 24-36 h relisting for retransplantation must be considered in order to avoid the development of multi-organ failure, in which case the mortality rate associated with retransplantation is very high^[42].

Small-for-size syndrome

Small-for-size syndrome has often been described in patients receiving a split liver or a partial liver graft from a live donor. Clinical presentation includes delayed synthetic function, poor bile production, cholestasis, and susceptibility to other complications including sepsis^[41]. It is believed that portal hypertension and congestion in a small graft are the cause of this syndrome. Supportive care and avoidance of infectious complications are critical for graft recovery and patient survival^[43].

Vascular thrombosis

Hepatic artery thrombosis (HAT) is a potentially life-threatening complication which is not very common in adults but relatively frequent (1.5 to 25%) in children and in grafts where there is a size discrepancy between the donor artery and the native vessel^[44]. Causes of HAT include poor arterial flow, increased sinusoidal resistance, preservation injury, stenosis of anastomosis and hypercoagulability. HAT at an early stage typically leads to ischemia-necrosis of the graft, sudden deterioration in hemodynamics, severe coagulopathy, and marked elevation of aminotransferases. Doppler ultrasound is the method for evaluating hepatic artery patency and arteriography is indicated when the vessel cannot be well identified. Arterial thrombectomy can be performed either by interventional radiology or surgical exploration. When revascularization fails urgent retransplantation is mandatory^[45]. Portal vein thrombosis is less common and mainly occurs as a result of pre-transplant portal vein thrombosis or technical problems. Clinical manifestations include persistent ascites, enteric congestion and bleeding. Doppler ultrasound followed by a traditional angiogram or magnetic resonance angiogram is usually diagnostic. Surgical thrombectomy or radiological intervention is required to save the graft and avoid life-threatening complications. Prophylactic heparin or warfarin is indicated for children at high risk of thrombosis.

Biliary complications

Biliary complications have been described as the “Achilles heel” of liver transplantation. Biliary leaks are a common consequence of necrosis at the surgical anastomosis, technical errors or biliary tract ischemia. They are very frequent in living donor liver transplantation^[46]. Lack of bile outflow through a drainage, an increase of cholestatic enzymes, and leucocytosis are indicative of a biliary complication. Ultrasound and/or abdominal CT scans may show ductal dilation or bile collection. The leak may resolve itself conservatively or may require treatment. Treatment options include endoscopic-retrograde pancreatography with biliary stenting or percutaneous transhepatic cholangiography with external drainage, or surgical repair.

Biliary obstruction can be caused by ischemia, technical problems, and small duct size from partial allografts^[47]. Biliary strictures are usually treated with endoscopic or percutaneous balloon dilatation, stenting, or surgical re-exploration.

Rejection

Acute rejection normally occurs 7-14 d after the operation but can manifest earlier or much later. Hyperacute graft rejection is very rare in liver transplantation and is determined by preformed antibodies. Acute rejection is usually T-cell mediated and injures the bile ducts and vascular endothelium of the liver. Rejection is associated with graft dysfunction and negatively affects graft survival. Bilirubin and transaminases are always increased and the bile from a T-tube may become thin and lighter in color. Diagnosis is made through liver biopsy. Treatment depends on the severity of the rejection and the underlying diagnosis of the patient^[48]. Mild rejection may respond to an increase in baseline immunosuppressive doses, pulse steroids, the use of mycophenolate and/or a switch to tacrolimus if the patient was on cyclosporine. More severe rejections require repeated steroid boluses and/or antilymphocyte globulin. Rarely does acute rejection require retransplantation.

Post-operative bleeding and coagulopathy

Poor graft function, imperfect hemostasis, slippage of a tie, hypersplenism, hypocalcaemia and dilution may lead to bleeding which necessitates transfusion or surgical re-exploration. Intra-abdominal and wound “oozing” in the first post-operative hours may also result from heparin release from the implanted graft along with hyperfibrinolysis.

The risk of bleeding is increased by thrombocytopenia, mainly caused by platelet activation-consumption and sequestration following graft reperfusion, and platelet-associated immunoglobulin M and immunoglobulin A antibody production. Other causes of thrombocytopenia include viral infection, cytomegalovirus-induced hemophagocytic histiocytosis, and treatment with antiviral therapy. Thrombocytopenia usually regresses within two weeks, but in some individuals it lasts longer due to persistent splenomegaly.

Monitoring of coagulation by thrombelastography (TEG) becomes necessary in cases of significant and persistent bleeding. TEG can be useful in differentiating between bleeding secondary to incomplete surgical hemostasis, platelet dysfunction and anomalies in coagulation factors^[49]. Besides helping to optimize blood component administration TEG is also useful in assessing graft function. Whereas the replacement of blood products is usually sufficient to compensate for moderate post-operative hemorrhage, in the presence of severe coagulation abnormalities even the massive infusion of hemostatic components along with antifibrinolytic drugs proves ineffective. The administration of recombinant factor VIIa (rFVIIa, Novo-seven[®], Novo Nordisk), which results in localized thrombin generation and does not lead to systemic coagulation or fibrinolysis, has been shown to improve hemostasis and reduce transfusion requirements during OLTx^[50]. The efficacy and safety of rFVIIa in the rescue management of a critical perioperative bleeding have been reported on many occasions^[51]. Patients who received rFVIIa did not experience a greater rate of thromboembolic events in comparison with the control groups.

In the management of post-operative hemorrhage the risk of bleeding must be balanced against the risk of hepatic artery or portal vein thrombosis. For this reason, overcorrection with fresh frozen plasma or platelets should be avoided. Platelets play an important role in the imbalance between prohemostatic and antihemostatic pathways during the first day after OLTx, probably contributing to thrombotic complications^[52]. According to some authors^[53] platelets transfusion should only be performed in cases of active-prolonged bleeding or when platelet count is $< 20 \times 10^9/L$. Other authors, conversely, adopt a more “aggressive” approach in treating post-operative coagulopathy, and suggest maintenance of an INR between 1.5 and 2, a platelet count $> 50 \times 10^9/L$ and a fibrinogen level $> 100 \text{ mg/dL}$.^[54]

Neurological complications

Careful evaluation of a patient’s mental status should be constantly performed during the ICU stay as neurological complications are very common after OLTx. Clinical series have documented neurological disorders in 8.3% to 47% of all patients receiving liver transplantation^[55]. The most frequent complications are encephalopathy, brain hemorrhage, and seizure. Patients with neurologic symptoms prior to transplantation are at greater risk for post-operative neurologic disturbances. A poor graft function may result in recurrence of encephalopathy. The etiology of encephalopathy is often difficult to determine as multiple factors such as subarachnoid hemorrhage, meningitis, infarction, spinal cord necrosis and cytomegalovirus infection may be involved^[56].

Seizures are the second most common neurological complications reported in liver transplanted patients. Seizures may be a consequence of factors including stroke, metabolic disturbances, electrolyte disorders, drug toxicity, previous history of epileptic seizures, central nervous sys-

tem infection and are often preceded by some degree of encephalopathy^[57].

Infections involving the nervous system are responsible for about 10% of post-operative neurological disturbances. Infections can either occur in the context of cerebral hemorrhage or systemically with subsequent neurological involvement. *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Candida* and *Aspergillus* are the pathogens commonly involved in the central nervous system infections^[58]. Anoxic-ischemic events occur early in the post-operative course and are often preceded by transient or varying degrees of hypotension. Hemorrhage and infarcts can occur within 1 wk or up to 1 mo after transplantation, and are sometimes associated with bacteremia and/or fungemia. The frontal and parietal lobes of the central nervous system are mainly affected by hemorrhage. Psychosis is another feared complication of OLTx. It has a multi-factorial etiology, but often is a consequence of prolonged ICU stay, use of steroids or other immunosuppressants, and adverse drug interactions^[59].

Immunosuppression-related neurological manifestations may develop following high-dose steroids and calcineurin inhibitors, which can lower the seizure threshold. Neurological disturbances induced by immunosuppressive treatment include headache, confusion/psychosis, speech apraxia, action myoclonus, visual hallucinations, tremor, delirium, cortical blindness, and coma.

Posterior leukoencephalopathy is a severe, rare and usually reversible syndrome, characterized by occipital and parietal extra-pontine demyelination (triggered by reactive astrocytosis and a neuronal loss), which is likely due to calcineurin inhibitors^[60].

Central pontine myelinolysis is one of the most severe neurological problems of OLTx, with a frequency after transplant of about 1–3.5%^[55]. It is characterized by symmetrical loss of myelin at the base of the pons, and develops, albeit not solely, following a rapid correction of prolonged hyponatremia^[61].

Conditions which increase the risk of post-operative neurological impairment also include pre-existing blood-brain-barrier alterations causing toxic intracerebral drug levels, dysmetabolic alterations (e.g. hyperglycaemia and hypocholesterolemia), and electrolyte and osmotic disorders (hyperosmolar syndrome)^[56].

Renal dysfunction

The true incidence of renal failure after OLTx is not known due to the differences in the criteria and methods applied to evaluate renal function. It has been reported to vary from 5 to 50% with 8%-17% of recipients in need for renal replacement therapy^[62].

The critical clinical state before transplant, intraoperative hemodynamic disturbances, massive transfusion, and many post-operative adverse events, such as infections, surgical re-exploration, and radiological investigations are frequently involved in the development of acute renal failure.

Post-operative renal dysfunction probably also occurs in the case of pre-transplant hepato-renal syndrome, graft

dysfunction, prolonged use of vasoactive agents, and drug-induced tubular-injury (cyclosporine, tacrolimus, amphotericin, aminoglycosides etc.)^[63].

Accurate monitoring of intake and outputs and the avoidance of toxic drugs is critical in the immediate post-operative period. Oliguria may be the earliest warning sign of renal dysfunction. Most renal insults are mild and mainly caused by reversible hemodynamic-mediated reductions in glomerular filtration rate. Conversely, severe renal dysfunction requiring dialysis can greatly affect the immediate outcome. Continuous assessment of volume status by dynamic volumetric measurements may prevent an excessively negative fluid balance, renal vasoconstriction and tubular hypoperfusion, and large requirement for vasoactive agents. The so-called reno-protective agents like dopamine, calcium channel blockers or prostaglandins have not been proven to be of value in preventing or treating post-operative renal failure^[63]. Reducing the dosage of calcineurin inhibitors or delaying their introduction has been found useful in long-term renal protection. Alternative immunosuppressive agents such as sirolimus and everolimus, and/or mycophenolate mofetil should be considered in at-risk patients in order to replace or minimize calcineurin inhibitor use^[64,65].

Antifungal Amphotericin B may not be devoid of renal consequences and agents such as voriconazole or echinocandins, when indicated, should be preferred.

Prophylactic administration of fenoldopam has been reported to reduce the risk of acute renal failure by counterbalancing the vasoconstrictive effect of cyclosporine and the maintenance of perioperative renal vasodilation^[66,67].

When renal dysfunction is severe enough to induce fluid retention and/or metabolic or electrolyte disturbances, dialysis or preferably lactate-free continuous renal replacement therapy (CRRT) is required until spontaneous recovery of tubular function. Compared to dialysis, the continuous replacement techniques result in less dramatic fluid shifts and changes in osmotic gradients and they are, therefore, also safe on hemodynamically unstable patients.

CONCLUSION

OLTx has become an effective and valuable option for patients with end stage liver disease. However, the ICU morbidity associated with some unpredictable factors such as a difficult intraoperative course, delayed post-operative hemodynamic recovery, “marginality” of the implanted graft, and “distant” organ dysfunction is still substantial. A better understanding and management of immunosuppressive therapy along with a more effective post-operative care have improved the outcome even in recipients with very advanced stages of liver failure. Various reports have demonstrated that the transplantation of sicker patients has not been associated with a reduction in post-OLTx graft and patient survival^[68,69].

Through prevention, recognition, and prompt treatment of life-threatening events, liver transplant recipients may experience fewer post-operative complications, shorter length of ICU stay, and a better overall outcome.

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