REVIEW ARTICLE

Intensive care management in adult liver transplantation

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ABSTRACT

Postoperative intensive care management of transplanted cases has shown a rapid development since the introduction of liver transplantation (LT). While one-year survival rate after LT was 79% in 1998, it raised to 90% in 2008, and while ten-year survival rate was 33% in 1998, it raised to 66% in 2010 owing to improvements in preoperative optimization, surgical technique, intraoperative anesthesia management, organ preservation, intensive care and immunosuppressive treatment. Rapid hemodynamic stabilization, correction of severe coagulopathy, respiratory stabilization and early weaning from mechanical ventilation, appropriate fluid-electrolyte therapy, preservation of renal function, prevention of graft rejection and prophylaxis/treatment of infection are particularly important in intensive care management of liver transplanted patients. Since early postoperative period is critical, close monitoring, stabilization and maintenance of cardiorespiratory functions, frequent examination of graft function, early identification of complications and prompt treatment of extrahepatic organ failure are mandatory in order to reduce mortality/morbidity.

Key words: Liver transplantation; Postoperative period; Intensive care; Liver failure

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INTRODUCTION

Intensive care management of liver transplanted patients requires sophisticated monitoring and multi-disciplinary approach. For an ideal intensive care treatment today, an experienced team (doctor, nurse, physiotherapist etc.) and advanced intensive care/institution facilities (diagnostic-treatment devices, operating room, blood bank, pharmacy etc.) are mandatory.[1] Postoperative intensive care management of transplanted cases has shown a rapid development since the introduction of liver transplantation (LT). While one-year survival rate after LT was 79% in 1998, it rose to 90% in 2008, and while ten-year survival rate was 33% in 1998, it rose to 66% in 2010 owing to improvements in preoperative optimization, surgical technique, intraoperative anesthesia management, organ preservation, intensive care and immunosuppressive treatment.[2,3]

A great extent of liver transplanted patients are monitored in intensive care unit (ICU) in postoperative period.[4] Although some studies report that patients who are stable during surgery and who do not develop complications have been monitored in postanesthesia care unit (PACU) without admission to ICU, and have been transported to their wards afterwards, most patients are admitted to ICU being either intubated or extubated.[5] Patients' ICU stay length vary depending on their postoperative conditions, intraoperative course and postoperative development of complications.6 Average ICU stay length following LT has shortened significantly owing to advancements in departments related to transplantation (surgery, anesthesia, intensive care, immunology etc.). In a related review published in 1994, average postoperative mechanical ventilation duration was reported as 36 hours and average ICU stay length was reported as 6 days, whereas today it is reported that average ICU stay length in many institutions has shortened to less than 24 hours for cases who do not have any complications, and yet more, selected cases in some institutions are transported to ward without ICU admission after monitoring and stabilization in PACU.[5,7,8]

In fact, anesthesia management and postoperative intensive care management are integral for liver transplantation. Matters primarily related to anesthesia management such as intraoperative hemodynamic monitoring choice, intraoperative fluid balance and extubation in operating room principally influence postoperative care of recipient and graft.[9] Rapid hemodynamic stabilization, correction of severe coagulopathy, respiratory stabilization and early weaning from mechanical ventilation, appropriate fluid-electrolyte therapy, preservation of renal functions, prevention of graft rejection and prophylaxis/treatment

of infection are particularly important in intensive care management of liver transplanted patients.[10]

There are several perioperative factors which have an influence on the outcome of LT. Preoperative condition of the recipient, intraoperative surgical course, quality of the liver graft, postoperative infection development, side effects of immunosuppressive drugs are the important determinants of the outcome. Although severity of preoperative condition of the recipient is inversely related with survival, as this is not the sole determinant, LT can be successful even in critical patients with high scores for MELD (*Model for End-Stage Liver Disease*) and APACHE (*Acute Physiology and Chronic Health Evaluation*).[11,12] According to *D-MELD* model that is based on recipient's age and preoperative MELD score, higher scores (*D-MELD*>1600) have been associated with shorter graft life in the short and long terms.[13]

GENERAL PRINCIPLES

Arterial blood pressure (ABP), electrocardiogram (ECG), peripheral oxygen saturation (SpO_2), central venous pressure (CVP) and/or pulmonary artery pressure/capillary wedge pressure (PAP/PCPW) depending on the intraoperative choice and body temperature are continuously monitored and urinary output is checked hourly. Patients are generally hypothermic so heat loss should be prevented and patients should be actively warmed immediately. After checking for vital functions and monitoring all drains, catheters (nasogastric, bladder, intraabdominal, biliary etc.) should be emptied and recorded, and monitoring started. 12-lead ECG and chest X-ray are performed in all patients and are repeated as required. Laboratory workup include arterial blood gases (ABG), complete blood count (Hb, leukocyte and thrombocyte count), coagulation panel (prothrombin time, INR, aPTT, fibrinogen), electrolytes (Na, K, Ca, Cl, Mg, P), metabolic panel (blood glucose, urea, creatinine, AST, ALT, bilirubin, ALP, GGT, LDH, albumin, ammonia, lactate), these are repeated every 6-12 hours depending on patient's condition. Samples for cultures of blood, urine, tracheal secretions and drain fluid are obtained as required. Following initiation of immunosuppressive treatment, therapeutic drug monitoring is performed and adjustments are made as necessary.[1,14]

Head of the bed is raised 30°- 45° in normotensive patients. For patients who will not be extubated soon, sedoanalgesia is administered with short-acting and non-hepato/nephro-toxic drugs (propofol, remifentanil, fentanyl etc.) in boluses or continuous infusion depending on the patient's condition. Prophylactic antibiotic therapy (usually 3rd generation cephalosporins and oral nystatin) and immunosuppressive therapy should be initiated in the early postoperative period according to institutional protocol, observing renal functions. Anticoagulation is initiated particularly in risky patients who have previously known hypercoagulopathies (Budd-Chiari, Protein C and S deficiency) and pediatric cases in some centers with low dose unfractionated heparin (100-200 U/kg/d, IV infusion in 24 hours), while in others anticoagulation is prophylactically administered in all patients. Blood flow in hepatic artery and portal vein should be examined daily with Doppler ultrasonography (USG) especially during the first three days, and should be repeated as required. Following the acute phase after LT (hemodynamic and respiratory stabilization), most important problems encountered in ICU are infectious complications, renal failure, prolonged mechanical ventilation due to pulmonary problems and graft dysfunction.[4,6,9]

CARDIOVASCULAR PROBLEMS & HEMODYNAMIC MANAGEMENT

In cases who had end-stage liver disease (ESLD), cardiovascular problems that existed at the preoperative period continue to be a problem at intraoperative and postoperative periods and determine the hemodynamic management. These patients have a hyperdynamic circulation characterized by increased cardiac output (CO), decreased systemic vascular resistance (SVR) and relatively decreased intravascular volume. Many cases also have cirrhotic cardiomyopathy; and although cardiac output is increased, hypotension or acute congestive heart failure is common due to impaired vena cava clampage, reperfusion, acidosis, hypocalcemia, hypervolemia etc.).[15,16] Following liver transplantation, SVR increases after an average of 48 hours, and CO decreases after 64 hours; both signs indicate a well-functioning graft.[17] However, it takes about 2-6 months period after LT for the hyperdynamic circulation to return to normal completely.[18,19]

Hemodynamic monitoring of the cases following LT is made by monitoring with invasive ABP, ECG, CVP and/or PAP/PCWP, CO depending on the intraoperative choice. Since there is no consensus on hemodynamic monitoring in LT yet, facilities of the center and experience of anesthetists are decisive. While some centers perform pulmonary artery catheterization (PAC) routinely, others mostly use CVP monitoring only and perform PAC in selected cases. Recent trend in hemodynamic monitoring is towards less invasive, continuous rather than instantaneous, and functional rather static monitoring. Therefore PAC has declined in the last 10 years compared to past.[20] However, there are studies stating PAC as gold standard for hemodynamic monitoring in LT.[21] PAC is particularly required for hemodynamic management of cases with porto-pulmonary hypertension (PPH).[22]

The main purpose in hemodynamic management is to maintain a safe mean artery pressure (MAP) required for optimal organ perfusion, particularly for liver and kidneys.

Generally accepted MAP is 70 mmHg and above.[23] Some reasons for hypotension developing at postoperative period are hypovolemia, prolonged reperfusion syndrome, left ventricular dysfunction, hypocalcemia, myocardial ischemia and vasodilation due to active warming.[10] Hypotension secondary to hypovolemia is common at early postoperative period. Main reasons of hypovolemia are surgical bleeding, fluid shift to third space due to hypoalbuminemia and targeting low CVP (≤ 5 mmHg) values intraoperatively to reduce intraoperative bleeding.[24] Fluid replacement therapy is administered in many cases for this reason, using crystalloid solutions with albumin solution and blood products as required. There is no consensus for a target CVP value in fluid replacement therapy. While fluid replacement is done aiming CVP at 10-12 mmHg (in presence of PAC, aiming PCWP at 15 mmHg) in many centers, in some other centers especially transplantation surgeons desire lower CVP (≤ 5 mmHg) values to prevent liver graft congestion. However, there are studies indicating the liver graft perfusion and function are not compromised even at CVP values ≥ 5 mmHg.[25,26] Therefore, the purpose of fluid replacement is not to maintain a certain CVP value, but to achieve a value that provides target MAP (> 70 mmHg), sufficient hourly diuresis (1 ml/kg/hr) and optimum liver graft perfusion. A vasopressor agent, e.g. dopamine, adrenaline, noradrenaline, vasopressin, terlipressin, or methylene blue infusions may be used for this purpose; however, noradrenaline infusion (0.01-1 μg/kg/min), and vasopressin (0.5-6 U/hr)/ terlipressin (1.5 μg/kg/hr) infusions for their portal pressure lowering effects, have been administered more frequently in recent years. Ephedrine can be used in acute hypotension as 5-20 mg IV bolus.[2,27-31] It may not be possible to increase SVR or decrease vasopressor doses in graft dysfunction. Hypocalcemia (secondary to citrate intoxication due to massive transfusion), acute left ventricular dysfunction due to various reasons (hypervolemia, acidosis, hypothermia) on the ground of cirrhotic cardiomyopathy, and acute myocardial infarction may lead to decreased CO and hypotension that is resistant to vasopressor treatment. Inotropic agents like dopamine (5-10 μg/kg/min) and dobutamine (5-20 μg/kg/min), diuretics and vasodilator agents at low doses to reduce afterload, watching carefully for hypotension, can be added to the treatment in left ventricular dysfunction.10 Blood ionized calcium level is maintained over 0.9 mmol/L. The target of hemodynamic management is to maintain a safe MAP (> 70 mmHg) value and optimum organ perfusion particularly for liver graft and kidneys. Assessment of blood lactate levels and especially lactate clearance are very important for monitoring organ perfusion. Hyperlactatemia (> 1.5 mmol/L) in LT occurs as a result of two main reasons; anaerobic glycolysis due to tissue hypoxia; and inadequate lactate clearance by the dysfunctional liver. Momentary increases in lactate levels do not help to differentiate these two reasons; however continuous hyperlactatemia requires further investigation. On the other hand, increased lactate clearance is an indicator of well-functioning liver graft.[20,32]

Postoperative subclinical pulmonary edema is not an uncommon problem after LT; it occurs at least in 50% of cases within the first 24 hours. Acute left ventricular dysfunction due to various reasons (hypervolemia, acidosis, hypothermia) on the ground of cirrhotic cardiomyopathy, rapid increase in afterload due to prompt normalization of SVR and high doses of vasopressor agents may cause pulmonary edema and lead to respiratory compromise and graft hypoxia. Pulmonary edema should be rapidly treated depending on the etiology.[10]

Porto-pulmonary hypertension is diagnosed by mean pulmonary artery pressure (mPAP) increasing above 25 mmHg at rest or above 30 mmHg during exercise, and pulmonary vascular resistance being greater than 240 dyne/s/cm^{-5} with PCWP lower than 15 mmHg. Incidence of PPH among patients waiting for LT is 2-10%.[2] Oxygen treatment to maintain oxygen saturation above 90%, avoidance of hypervolemia with low dose diuretics, pulmonary vasodilators, IV prostacycline (epoprostenol), per orum sildenafil and inhaled iloprost; or if these are not available, nitrate (perlinganit®) infusion while watching for systemic hypotension, can be used in PPH treatment.[33]

Postoperative systemic hypertension can develop as a result of hypervolemia, severe anxiety, tremor, hypothermia, tacrolimus/cyclosporine and corticosteroid treatment, and uncontrolled vasopressor administration. Since uncontrolled hypertension can cause intracranial and intraabdominal hemorrhage, rupture of hepatic artery anostomosis and graft congestion, systolic blood pressures above 160 mmHg and diastolic blood pressures above 100 mmHg should be avoided.[1,4] Hydralazine, beta-blockers (esmolol, metprolol), calcium channel blockers (diltiazem, nicardipine) and sodium nitroprusside or nitrate infusions with invasive ABP monitoring can be used in its treatment.

Dysrhythmias, particularly atrial fibrillation can be observed in liver transplanted patients. Reasons for dysrhythmias include electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), hypoxemia, anemia, fluid overload, hypothermia, myocardial ischemia, high dose inotropic agents and inadequate sedoanalgesia. Treatment of the underlying cause (anemia, electrolyte disturbance etc.) is sufficient most of the time. For cases in whom dysrhythmia cannot be controlled despite these measures; appropriate anti-arrhythmic drugs depending on the type of dysrhythmia, electrical cardioversion and pacemakers can be administered. For complex and resistant dysrhythmias, cardiology consultation should be requested without delay.[1]

FLUID THERAPY & ELECTROLYTE-GLUCOSE BALANCE

Fluid Therapy

Major reasons of hypovolemia at the early postoperative period are surgical bleeding, fluid loss to third-space and interstitial space due to decreased oncotic pressure secondary to hypoalbuminemia, and targeting lower intraoperative CVP (≤ 5 mmHg) levels in order to reduce surgical bleeding which leads to a negative fluid balance at the time of ICU admission.[24] Therefore, fluid replacement therapy is administered in many cases using crystalloid solutions with albumin solution and blood products as required. Preferred crystalloid solution in patients with hepatic insufficiency should be serum physiologic (0.9% NaCl); and lactated ringer solutions (Hartmann sol.) should be avoided due to their lactate content. Lactate is converted to glucose in liver by Cori cycle, by-producing bicarbonate which causes alkalosis; however lactate metabolization is impaired in hepatic insufficiency; this may result in lactate accumulation and lactic acidosis. Rapid infusion of serum physiologic solution in great amounts (>3 L) can lead to hyperchloremic metabolic acidosis; therefore balanced electrolyte solutions containing acetate and gluconate instead of lactate (Isolyte S®- Plasmalyte®) can be used as an alternative to lactated ringer solution when required.2 It has been shown that synthetic colloids (HES, Gelatin) might cause renal failure and coagulation abnormalities; hence, as with all critical care patients, their use is not recommended in liver transplanted patients in accordance with recent guidelines and findings reported in literature.[34,35] As for natural colloids, albumin solutions can be used in liver transplanted patients with hypoalbuminemia (< 2.5 g/dL) in order to control peripheral edema and ascites development and to replace the loss from drains.[36-38] Instead of targeting a certain CVP level in fluid replacement therapy, it should be aimed to stabilize hemodynamics (MAP>70 mmHg) and provide optimum organ (kidneys, liver graft) perfusion. Adequate hourly diuresis (1 ml/kg) and increased lactate clearance are indicators of optimum organ perfusion. Excessive fluid replacement can result in hypervolemia, water-sodium retention, capillary leakage syndrome and graft congestion; it has been shown that if the hemodynamics and organ perfusion are stable, keeping the patient in minimal negative fluid balance on the postoperative first day reduces early pulmonary complications and increases graft oxygenation.[39]

Electrolyte Balance

As in all major surgeries, electrolyte imbalances can occur after LT. Hyponatremia and hyperkalemia are common in patients with end stage liver disease at preoperative period. Postoperative electrolyte imbalances are mostly associated with nutritional status prior to LT, intraoperative problems and administered medications, intraoperative fluid loss and replacement, and transfusion of blood products containing citrate. Hyperkalemia, hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypomagnesemia, hypo/hyperglycemia are the common disturbances.[10]

Hyponatremia is one the most important of all electrolyte imbalances, which occurs as a result of rapid changes in plasma osmolarity. It is also common at preoperative period in LT patients using diuretics and/or who have fluid overload. Hyponatremia is one of the poor prognostic factors in LT; its rapid correction leads to central pontine myelinolysis. Avoidance of rapid changes in sodium level should be an essential target at perioperative period. In chronic hyponatremic patients without neurological signs, hypertonic saline (3% NaCl) administration should be avoided unless serum sodium level drops below 120 mmol/L. In case it is indicated, hypertonic saline treatment can be administered while keeping the rate of increase in serum sodium below 0.5 mmol/L, targeting a serum sodium level of 130 mmol/L. Otherwise fluid restriction and hydration with serum physiological (0.9%) are sufficient.1,40-43

Hypernatremia is less common; its causes include dehydration, diuretics, administration of salt-rich solutions (albumin sol.) in large amounts, uncontrolled hypertonic saline administration. Treatment depends on the etiology and low sodium content solutions as 0.45% NaCl are used for fluid replacement when needed.

Hyperkelamia can be observed in LT patients depending on preoperative high basal levels, duration of intensive care stay of the organ donor, whole blood and erythrocyte suspension (ES) transfusions, high potassium content of the organ preservation solutions (especially, University of Wisconsin.UW] solution), warm ischemia time, use of veno-venous bypass, acute renal injury, immunosuppressive treatment (cyclosporine, tacrolimus) and primary graft dysfunction. In patients who have preoperative renal insufficiency (hepatorenal syndrome), hyperkalemia especially occurring after transplantation needs urgent treatment. Preoperative potassium level in the recipient has been shown to be associated with mortality in LT.[44] Insulin/glucose, bicarbonate, furosemide, beta agonists and calcium can be used in pharmacological treatment; however, early hemodialysis is necessary for resistant elevations (>6.5 mmol/L) and if the patient is oliguric/anuric.[45]

Hypokalemia can develop in LT patients as a result of metabolic alkalosis, hypothermia, certain medications (furosemide, insulin, corticosteroid, amphotericin B etc.) and insufficient replacement. It is usually together with hypomagnesemia; and since it is difficult to correct hypokalemia in the presence of hypomagnesemia, intravenous (IV) magnesium replacement should be

administered. Phosphate levels should also be checked, and if there is hypophosphatemia, IV potassium replacement can be done using potassium phosphate preparations. If phosphate level is normal, potassium chloride preparation is used.[1,14,44,46]

Hypocalcemia is common in LT patients. Particularly rapid transfusion of blood products containing citrate (ES, fresh frozen plasma.FFP]) intraoperatively is the leading cause of hypocalcemia. For this reason, close monitoring and replacement of ionized calcium during LT is very important with regards to cardiovascular stability and normal coagulation. Metabolic alkalosis is another reason for hypocalcemia. One important point in monitoring of blood calcium level is that changes in albumin level effect total calcium levels. Since hypoalbuminemia is common in LT patients, monitoring for calcium levels must either be performed with ionized calcium or correction must be made for total calcium levels. Calcium replacement should be made with IV calcium gluconate/calcium chloride preparations in order to maintain ionized calcium levels at >0.9 mmol/L.[1,47]

Hypomagnesemia is another common electrolyte imbalance in LT patients. Many patients also have hypomagnesemia before LT due to malnutrition; and it becomes more pronounced with rapid transfusion of blood products, metabolic alkalosis and certain medications (furosemide, cyclosporine, tacrolimus) at the perioperative period. Hypomagnesemia is usually together with hypokalemia and hypocalcemia. Hypokalemia and hypomagnesemia are the most important causes of perioperative dysrhythmia. Tetany, muscle pain and convulsions are some clinical findings of hypomagnesemia and IV magnesium replacement is administered in its treatment while monitoring blood magnesium levels.[1,46]

Hypophosphatemia makes difficulty in weaning from mechanical ventilation by causing weakness in respiratory muscles. It also causes thrombocyte dysfunction, disturbance in myocardial contractility and neuromuscular irritability. Replacement therapy can be done in severe hypophosphatemia (<1.5 mg/dL) with potassium phosphate preparations; however, should be alert for hyperkalemia.

Hypermagnesemia, hypercalcemia and hyperphosphatemia are less common electrolyte disturbances in LT. They usually occur iatrogenically due to excess replacement in liver transplanted patients. Hypermagnesemia and hyperphosphatemia can also be observed in renal insufficiency.

Glucose Balance

A normal glucose metabolism following LT indicates a well-functioning graft. Hypoglycemia is an indicator of deterioration in the hepatic recovery, and it is common in primary non-functioning graft (PNF). Hyperglycemia is a common disturbance, and the leading cause is preoperative diabetes mellitus in the recipient. Other causes of hyperglycemia are corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus), surgical stress and postoperative infections (sepsis). In diabetic recipients, glucose metabolism is further compromised during LT, progressive hyperglycemia can develop particularly in reperfusion period. Hyperglycemia is known to increase ischemic reperfusion damage in many organ systems, so intraoperative control of blood glucose levels is important in LT.[10,48] Severe hyperglycemia (glucose >200 mg/dL) has been associated with increased hepatic graft rejection, surgical site infection and mortality.49-52 Recent studies and guidelines recommend maintaining blood glucose levels as <180 mg/dL in intensive care, rather than strict glucose control (80-110 mg/dL). For treatment of hyperglycemia, crystalline insulin infusion should be administered in order maintain blood glucose levels as <180 mg/dL, while watching for hypokalemia and hypoglycemia.[53,54]

POSTOPERATIVE BLEEDING & TRANSFUSION

Causes of bleeding at early postoperative period include coagulopathy, thrombocytopenia, hypocalcemia, hypothermia, PNF, laceration on liver surface, anastomosis leak, heparin-related bleeding, hepatic artery stenosis (HAS) and hepatic artery thrombosis (HAT), invasive interventions (liver biopsy etc.). Postoperative bleeding in LT patients has been reported in the rates of 7% to 15%. While 50% of the bleeding developing after LT had been controlled surgically in the past, today this rate has decreased to 10-15% owing to more efficient treatment of coagulopathy in intensive care. Diagnosis of postoperative bleeding is essentially clinical. Clinical signs as tachycardia, hypotension, reduction in CVP, abdominal distention, reduced hourly diuresis (oliguria), blood coming from the abdominal drains (may not always be the case) raise suspicion about postoperative bleeding; definitive diagnosis is made by laboratory results including decreased hemoglobin level, decreased mixed venous oxygen saturation, abdominal USG and abdominal angio-tomography. First step in the treatment is to correct severe coagulopathy; if hemodynamics still cannot be stabilized and if there has been need for ES transfusion that is greater than 4-6 units within 24 hours, surgery (re-operation) is indicated.[1,4,14,55]

Coagulation profiles of LT patients can show a wide range of variation from normal (hepatocellular carcinoma) to severe coagulopathy (fulminant liver failure). According to some authors, coagulopathy occurring in liver failure is a balanced coagulopathy where pro-coagulant and anti-coagulant factors decrease in the same proportion; and

bleeding, thrombosis or both of them can be observed depending on the course of complications (renal failure, infection etc.).[2,56,57] Therefore rapid and sensitive monitoring of the coagulation system is required at the perioperative period of LT. Classical coagulation tests (PT, aPTT) have limited value in LT because their turnaround time is long, and they only reflect the procoagulant pathway without evaluation of thrombocyte functions and fibrinolysis. Rational use of blood products and pharmacological agents depend on rapid and sensitive point-of-care monitoring of the coagulation system. Thromboelastogram (TEG) and rotational thromboelastometry (ROTEM) are two point-of-care methods enabling rapid and sensitive evaluation of coagulation system in LT. These methods reflect all steps in development of thrombus and also fibrinolysis, thereby they enable rational administration of transfusion and medications (anti-fibrinolytics, coagulation factors, etc.), and reduce the need for transfusion of blood products in LT.[57-59]

There are several factors causing coagulopathy at perioperative period in LT such as hypothermia, acidosis, hypocalcemia, uremia, citrate intoxication, hemodilution and hyperfibrinolysis. If preventive measures for heat loss and active warming applications have been inadequate particularly at the intraoperative period, then hypothermia is inevitable in postoperative period. Hypothermia has been shown to affect coagulation system adversely even if plasma coagulation factors are normal, therefore heat loss at the intraoperative period should be prevented and normothermia (>36 C°) should be aimed for. Excess transfusion of blood products (ES, FFP) results in citrate intoxication and hypocalcemia, which may cause coagulopathy; therefore, perioperative transfusion therapy should be performed rationally, and blood ionized calcium levels should be monitored and replaced as necessary to keep it >0.9 mmol/L. As another important factor, arterial blood pH value should be monitored as well and it should be kept within normal limits.[47,60,61] Leak from intraabdominal and surgical incision sites could occur within postoperative first few hours due to heparin release from liver graft and hyperfibrinolysis. Bleeding risk is further increased in case of thrombocytopenia.[10]

There is no generally accepted evidence-based threshold values (Hb, thrombocyte, INR, aPTT) for transfusion of blood products that is valid in all centers with regard to liver transplantation. However, there are many evidences on the association of transfusion of blood products (ES, FFP, thrombocyte suspension.TS]) with increased morbidity/mortality (increased rates of transfusion related acute lung injury.TRALI], infection, HAT, etc,) and readmission to ICU.[62-68] For that reason, recent guidelines restrict the use of blood products substantially. Today, the recommended threshold level of hemoglobin (Hb) for blood transfusion is 7 g/dL for patients who are hemodynamically stable and without any risk factors. In case there are risk factors such as ischemic heart disease or brain damage, this threshold level may increase up to 9 g/dL. In summary, target perioperative Hb levels should be 7-9 g/dL depending on patient's condition. Optimization of cardiac output, ventilation and oxygenation make it easier to tolerate low Hb levels.[47,48,54,60,69] In management of postoperative coagulopathy, risk of bleeding should be counter-balanced with risk for HAT and portal vein thrombosis (PVT). Therefore, overcorrection of coagulopathy with transfusions of FFP and TS should be avoided. Viscoelastic tests (TEG-ROTEM) are recommended rather than the standard coagulation test in the management of coagulopathy treatment. According to some authors, thrombocytes play important role in thrombotic complications especially at the early postoperative period, so they recommend not to administer TS transfusions unless thrombocyte count drops to $< 20 \times 10^9$/L or there is active bleeding/leakage (despite other factors being normal). Prior to invasive interventions like liver biopsy and re-operation, thrombocytes should be replaced in order to maintain the thrombocyte count $>50\times10^9$/L. Similarly, according to recent conceptions, there is no need for FFP replacement in mild-moderate INR elevation (INR<2.0-2.5) unless there is active bleeding/leakage or re-operation is planned. In this manner, monitoring of graft functions is made more accurately without being affected from TS/FFP transfusions. Fibrinogen level should be replaced in case of active bleeding/leakage in order to keep its levels as >1.5-2.0 g/L, primarily with fibrinogen concentrate (25-50 mg/kg), or otherwise with cryoprecipitate (1-2 U/10 kg); fibrinogen levels should be at least >1 g/L prior to invasive interventions. On the contrary, some centers perform a more aggressive treatment for coagulopathy in order to maintain INR between 1.5-2.0, thrombocyte count $>50\times10^9$/L, and fibrinogen level >2g/L.[10,47,59,60,63,65,70]

Hyperfibrinolysis is a coagulopathy characterized by microvascular leakage that can be observed during anhepatic/neohepatic phases of liver transplantation and in the early postoperative period. Definitive diagnosis of hyperfibrinolysis is made with TEG/ROTEM methods. Antifibrinolytic agents are the recommended drugs if hyperfibrinolysis develops. These include tranexamic acid, epsilon-aminocaproic acid (EACA) and aprotinin. Aprotinin (Trasylol®) has recently gone out of production due to its side effects. Tranexamic acid, which has also been used prophylactically in LT previously, is nowadays recommended only when there is hyperfibrinolysis. The recommended dose of tranexamic acid is 20-25 mg/kg via infusion (in 10 minutes); repeating the same dose or continuous infusion as 1-2 mg/kg/hr following the initial dose is recommended as required. Antifibrinolytic agents have been reported not to increase thromboembolic

complications; however, their use should be avoided in risky patients with known hypercoagulopathies (Budd-Chiari, protein C and protein S deficiency, history of previous thromboembolic event). Activated recombinant factor VIIa (rFVIIa) could be used as a last measure in diffuse leakage/bleeding that is difficult to control (dose: 90-120 μg/kg IV); its prophylactic use is also not recommended due to increased risk for arterial thrombosis. Desmopressin may be considered in bleeding due to hereditary (von Willebrand disease) or uremic thrombocyte dysfunction. Recommended dose for desmopressin is 0.3 μg/kg IV/SC per 4-8 hours.[2,47,59,71-73] Deficiency of vitamin K-dependent coagulation factors (F II, FVII, FIX, FX) is common in ESLD; prothrombin complex concentrate (PCC) can be administered in that case, without causing volume overload. There is an ongoing randomized trial related to prophylactic use of PCC in order to reduce blood transfusion needs in LT.[74]

PULMONARY PROBLEMS & RESPIRATORY MANAGEMENT

Pulmonary complications developing at early postoperative period lead to increased infection risk by prolonging the duration of mechanical ventilation or by necessitating re-intubation. Most common pulmonary complications are pleural effusion, atelectasis, pulmonary edema, ventilator-associated pneumonia (VAP), acute respiratory failure and right diaphragm paralysis. Causes of postoperative atelectasis include pleural effusion, right diaphragm paralysis, bronchial obstruction, prolonged immobilization, insufficient inspiration due to postoperative pain and impaired clearance of secretions. Right diaphragm paralysis can occur when right phrenic nerve is injured during surgery, and it results in atelectasis of right lower lobe. Postoperative respiratory failure is one of the most common pulmonary problems that can cause mortality. Recipient's age and general preoperative condition (MELD score), hepatopulmonary syndrome (HPS), PPH, renal failure, hemodynamic instability, severe neurological impairment, preoperative mechanical ventilation, molecular adsorbent recirculating system (MARS) support, diabetes mellitus, deceased donor, chronic obstructive and restrictive lung diseases have been reported as preoperative risk factors associated with pulmonary problems. Reported intraoperative risk factors are properties of surgical intervention (large incision, mechanical trauma, prolonged surgery and/or graft ischemia time), excessive fluid and blood transfusion, positive fluid balance and severe reperfusion syndrome. Postoperative risk factors include prolonged mechanical ventilation, acute rejection of the graft or PNF, severe immune deficiency, acute renal failure, right diaphragm paralysis, hemodynamic instability, surgical complications and re-operation.[1,14,75-80]

In many centers, when LT is performed electively, patients are extubated in the operation room at the end of the operation if they are stable for cardiovascular, respiratory and metabolic aspects and meet extubation criteria, and they are then followed up in ICU; or less commonly they are monitored in PACU for a while and then admitted to ward in some centers.[5,81] Early extubation in appropriate patients has been shown to improve graft function, reduce ICU stay and costs and decrease nosocomial infection rate. Patient selection for early extubation has been reported to depend on duration of operation, amount of transfused blood products, patient's preoperative condition (MELD score), graft condition and ischemia time.[82-84]

Difficulty in weaning from mechanical ventilation in ICU mostly arise as a result of postoperative respiratory complications related with massive transfusion, pleural effusion, abdominal distention and intraabdominal hypertension, pneumonia, insufficient clearance of bronchial secretions and side effects of immunosuppressive treatment. For liberation from prolonged mechanical ventilation, it is recommended to pause sedoanalgesic drugs daily and commence spontaneous breathing trials. Frequency (number of breaths in one minute)/tidal volume (L) ratio being less than 105 (rapid and superficial respiration index) prior to extubation is one of the important predictors of extubation success. Non-invasive mechanical ventilation (NIV) support is recommended right after extubation particularly in cases who have borderline gas exchange in spontaneous breathing trials with T-tube. Non-invasive mechanical ventilation performed with pressure support and positive end-expirium pressure (PEEP) has been shown to prevent loss of vital capacity and development of atelectasis following extubation and improve oxygenation. In addition, NIV application reduces the need for sedoanalgesia and makes it easier to mobilize the patients. It has also been shown to decrease infection (VAP) risk and mortality. Prolonged mechanical ventilation leads to increases in VAP frequency, muscle atrophy, tracheal injury and mortality. In cases duration of mechanical ventilation exceed 7-14 days, and if the patient does not have adequate cooperation and airway reflexes, tracheotomy should be performed.[2,6,8,10,37,48,85-88]

Acute respiratory distress syndrome (ARDS) is one of the most severe respiratory problems occurring after LT. Severe reperfusion syndrome, massive transfusion, long operation time and infections at early period constitute important causes of ARDS. Massive transfusion-related ARDS is specifically called TRALI; antibodies present in blood donor (anti-HLA) reacting with the leukocyte (granulocyte) antigens (HLA) of the recipient are responsible in its pathophysiology. Management of respiratory complications including ARDS primarily involves supportive treatment (treatment of infection, oxygen

therapy, prevention of hypervolemia, drainage of massive pleural effusion and ascites, bronchoscopic aspiration etc.); however, in case there are signs of respiratory failure, invasive/non-invasive mechanical ventilation support should be initiated without delay. Invasive mechanical ventilation should be preferred in moderate-severe cases of ARDS, applying lung protective ventilation (low tidal volume.6 ml/kg, ideal body weight], high PEEP, plateau pressure <30 cmH_2O). Although some studies have reported that mechanical ventilation with high PEEP (>10 cmH_2O) compromises venous drainage of liver and leads to liver edema, and reduction of splanchnic perfusion and cardiac output, Saner, et al. showed that blood circulation of liver (hepatic vein-artery, portal vein) was not impaired in PEEP applications up to 15 cmH_2O. Hypercarbia should be avoided in cases with preoperative intracranial hypertension (hepatic coma), preferably applying ≤10 cmH_2O PEEP; however, PEEP application should be elevated up to 15 cmH_2O if there is refractory hypoxemia, while watching for hypotension. In unresponsive cases of refractory hypoxemia; neuromuscular blockade, recruitment maneuvers, prone positioning and inhaled pulmonary vasodilators (nitric oxide, iloprost) can be administered with extracorporeal membrane oxygenation (ECMO) as a last measure.[9,10,61,64,75,89-94]

Pulmonary edema and HPS are among causes of hypoxemia observed at the early postoperative period. Severe pulmonary edema does not occur unless there is acute fluid overload in the recipient in presence of acute severe left ventricular dysfunction or renal failure. On the other hand pulmonary edema that is not detected by clinical signs but manifests itself in chest X-ray, which cause mild impairment in gaseous exchange, are commonly observed. Causes of postoperative pulmonary edema include acute left ventricular failure, hypoalbuminemia, hypervolemia due to massive fluid and blood products transfusion, pulmonary capillary endothelial damage secondary to systemic inflammatory response, renal failure, high-volume thoracentesis (re-expansion edema) and reduced lymphatic circulation. Marked and prolonged pulmonary edema have been reported to increase ICU and mechanical ventilation durations. Hepatopulmonary syndrome is characterized by pulmonary vasodilation, hypoxemia with right to left shunt and increased alveolar-arterial gradient. Intrapulmonary vascular dilations are the main cause for hypoxemia that is observed in HPS. Although pulmonary angiography and therapeutic embolization are beneficial in selected cases, liver transplantation is the only cure for HPS. Improvement of the syndrome has been reported to start within days after transplantation, extending up to 15 months.[2,37,77,79,95-97]

Hepatic hydrothorax is pleural effusion that is characterized by single sided (generally right side) transudate exceeding 500 ml, that occurs in cirrhotic patients in the absence of a cardiac, pulmonary or pleural problem. It occurs as a result of transfer of the abdominal ascites through the defects in the diaphragm and impairment of diaphragmatic lymphatic drainage due to surgery. Hepatic hydrothorax can lead to respiratory distress and coughing in patients with spontaneous breathing, or in mechanically ventilated patients, it can impair ventilation by reducing lung compliance. Pleural effusions may increase in the postoperative first week; however, they usually resolve within the following weeks without any intervention. Pleural effusions that impair ventilation and cause marked atelectasis are drained with single punctures (thoracentesis) or by placing percutaneous catheter (pigtail); however, insertion of chest tubes are not recommended due to its complications. During thoracentesis, draining more than 1500 ml. at once should be avoided in effusions lasting more than 72 hours, in order to prevent development of re-expansion edema. Diffused abdominal ascites can lead to atelectasis and impaired ventilation by reducing expansion of the lungs. In this case, ascites is drained (paracentesis) in an amount sufficient to allow ventilation. After paracentesis, fluid /albumin replacement should be administered in patients, while monitoring urinary output, renal function tests and hemodynamic stability.[37,79,98]

Early extubation, respiratory physiotherapy and early mobilization after extubation, NIV application, adequate treatment of postoperative pain, prevention of hypervolemia, efficient clearance of bronchial secretions and prevention of infections have great importance in order to decrease postoperative pulmonary complications.[10,79,81,87,99]

RENAL PROBLEMS & MANAGEMENT

Renal dysfunction (RD) can develop despite every efforts in LT patients in the form of exacerbation (deterioration of the preoperatively existing dysfunction) or acute renal failure. Incidence of renal dysfunction has been reported to range between 5% to 50%; it has been reported that renal replacement therapy (RRT) is applied to 8% to 17% of the liver recipients. Approximately 10% of the patients with renal dysfunction develop end stage renal disease in the long term; therefore, early detection of patients carrying risk and prevention of RD are crucial. Important etiological factors postoperative RD include severity of the preoperative condition (MELD score), preoperative comorbities (diabetes mellitus, hepatorenal syndrome.HRS], chronic renal disease), intraoperative hemodynamic instability, massive transfusion, graft dysfunction, re-operation, intraabdominal hypertension, infections/sepsis, administration of nephrotoxic drugs (radiocontrast agents, calcineurin inhibitors, non-steroid anti-inflammatory drugs, aminoglycosides, amphotericin) and use of vasopressor agents at high doses for a long time.

Preoperative chronic creatinine elevation is an important predictor for postoperative RD development. Similarly, preoperative presence of HRS is an important cause of acute renal failure after LT. Since definitive treatment of HRS is LT, bridging treatments (IV albumin/terlipressin, trans-jugular intrahepatic portocaval shunt.TIPS], MARS applications) are used until transplantation. Following an unproblematic LT, HRS usually shows improvement within two to six weeks; however combined liver-kidney transplantation should be considered in patients who required hemodialysis for longer than 8-12 weeks prior to transplantation. It has been shown that pre-transplantation and postoperative RRT requirement is an independent predictor of mortality, and that mortality is higher in patients who required pre/post-operative RRT.[1,4,6,9,10,100-107]

Renal complications generally occur at the early period following LT. The most important reason for this is altered distribution between fluid compartments at the early period and thereby, development of relative hypovolemia. It has been shown that targeting low CVP (≤ 5 mmHg) in intraoperative period in order to reduce surgical bleeding has no negative effect on postoperative graft and kidney functions. Oliguria may be the first sign of RD. Close monitoring of fluid balance with hourly diuresis at the early postoperative period, correction of hypovolemia without delay by fluid (crystalloid/albumin) replacement and avoidance of nephrotoxic drugs have critical importance. Calcineurin inhibitors (cyclosporine, tacrolimus) are the most important reason for development of RD following an unproblematic LT. In case there are signs of RD emerging with these drugs, they should either be removed from the immunosuppressive treatment, or their doses should be lowered; and their dose must be adjusted by monitoring their serum levels. In patients who have high risk for postoperative RD development, it is recommended to use non-nephrotoxic agents (mycophenolate mofetil, sirolimus, everolimus) instead of calcineurin inhibitors, and to avoid other nephrotoxic drugs (radiocontrast agents, non-steroid anti-inflammatory drugs, aminoglycosides, amphotericin). Drug doses (immunosuppressives, antibiotics, digoxin, etc.) need to be adjusted according to serum levels and/or creatinine clearance in patients developing renal dysfunction. Studies have shown that prophylactic use of phenoldopam, which is a dopamine-receptor (D_1) agonist, provides perioperative renal vasodilation and decrease RD risk. It has been reported that renal dose dopamine (2-3 mcg/kg/min) administration does not have a renal protection effect, and that it can even lead to harm. Use of terlipressin in preoperative HRS treatment has been shown to reduce postoperative RD development.[1,6,10,108-114]

If RD is serious enough to cause fluid retention, metabolic disturbances (acidosis, encephalopathy, etc.) and electrolyte imbalances, hemodialysis or preferably continuous RRT without lactate should be administered (Table 1). When compared to hemodialysis, RRT techniques lead to less fluid shift and osmotic gradient changes; therefore, they are safer in hemodynamically non-stable patients and in cerebral edema. Hepatic encephalopathy, deceased donor, MELD score, intraoperative blood loss and LT due to hepatocellular carcinoma have been identified as independent predictors for postoperative RRT. Continuous RRT at perioperative (particularly intraoperative) period has been shown to be beneficial in the management of cardiovascular and metabolic instability and promote healing of renal functions postoperatively in patients with high risk for RD. Apart from continuous RRT, there are also centers which perform intraoperative hemodialysis and report favorable outcomes.[6,10,115-117]

Table 1: Indications for renal replacement therapy following liver transplantation

Biochemical Indications
Refractory Hyperkalemia (K^+ > 6.5 mmol/L)
Refractory Metabolic Acidosis (pH < 7.1)
Refractory hypo/hypernatremia, hypercalcemia
Clinical Indications
Marked oliguria (< 0.3 ml/kg/24 hours) or anuria (>12 hours)
Refractory hypervolemia
Uremic encephalopathy, pericarditis, bleeding
Renal dysfunction along with primary non-functioning graft

NEUROLOGICAL PROBLEMS / MANAGEMENT

Neurological complications can be observed in rates between 11% and 42% following liver transplantation in adults, the rate is lower in pediatric cases. They generally occur during the first month after transplantation; however, there have been cases of neurological complications observed up to 1 year (like tuberculous meningitis). Etiology of the neurological problems may originate at preoperative (hepatic encephalopathy, intracranial hypertension, metabolic disturbances), intraoperative (central pontine myelinolysis, cerebrovascular autoregulatory dysfunction, paradoxical cerebral emboli, metabolic disturbances) and postoperative (immunosuppressive toxicity, intracranial bleeding, graft dysfunction or PNF graft, cerebral infarct, central nervous system infections) periods. Neurological complications are separated into two group as major and minor complications. Major complications include encephalopathy, convulsions, intracranial bleeding, CNS infections, cerebellar syndrome, central pontine myelinolysis, cerebral infarction, posterior leukoencephalopathy, focal neurological deficits, vegetative state and toxic encephalopathies. Minor complications

include tremor, headache, sleep disorders, peripheral neuropathy and restless leg syndrome. Most commonly observed neurological complications are encephalopathy, convulsions and intracranial bleeding. Since LT related neurological complications are frequent, basal neuropsychiatric evaluation should be performed for each case prior to transplantation.[1,10,108,118,119]

Most neurological complications can be treated by correcting the etiological factors. Encephalopathy, which is the most frequent postoperative neurological problem, is closely related with preoperative hepatic encephalopathy and electrolyte disturbances (especially hyponatremia). Cases with preoperative hepatic encephalopathy can remain encephalopathic at the early postoperative period following LT, and are under risk for intracranial hypertension during the 48 hours following transplantation. In management of patients developing intracranial hypertension; 30^0 elevation of head, normocarbic ventilation (mild hyperventilation can be performed in short duration in acute intracranial hypertension), normovolemia, keeping MAP above the standard target (MAP>80-90 mmHg) in order to maintain optimum cerebral perfusion pressure, mannitol infusion (0.25-0.5 g/kg, IV bolus), inducing therapeutic hypernatremia with hypertonic saline infusion (target serum Na^+:145-155 mmol/L), mild hypothermia (34^0-36^0 C) are applied along with barbiturate coma and indomethacin (25 mg IV) as a last measure. Newly developing encephalopathy at the postoperative period may be associated with severe graft dysfunction, PNF graft, immunosuppressive toxicity (especially calcineurin inhibitors), subarachnoid hemorrhage, meningitis, cerebral infarction and cytomegalovirus infection.[2,10,120,121]

Convulsions are the second most common neurological problems that can occur after LT. Etiology of convulsions include cerebrovascular events, metabolic/electrolyte disturbances (hyponatremia, hypoglycemia etc.), immunosuppressive toxicity (especially calcineurin inhibitors), CNS infections and history of epilepsy. Correction of the underlying cause is the first step in its treatment, and anti-convulsive drugs (phenytoin, benzodiazepines, valproic acid, levetiracetam) are administered. Anticonvulsant drugs (phenytoin, phenobarbital) may decrease plasma levels of calcineurin inhibitors, so that their dose should be adjusted. Immunosuppressive neurotoxicity is related with administration of especially calcineurin inhibitors (cyclosporine, tacrolimus), OKT-3 and high dose corticosteroids. It can lead to a wide range of symptoms depending on the dose, such as mild tremor, speech disturbances, headache, confusion, psychosis, cortical blindness, myoclonus, convulsion, status epilepticus and coma. For its treatment, the drug dose should be lowered or it should be discontinued. Mycophenolate mofetil can be preferred in patients who develop severe neurological complication since it does not have a neurotoxic effect. Cerebral hemorrhages and infarctions occur within the first month (frequently first week) following LT. Cerebral hemorrhages have frequently been found to be associated with coagulopathy, advanced age and systemic infections (bacteremia/fungemia). Cerebral infarctions at perioperative period are mostly a result of hypoxic-ischemic injury that is secondary to hypotension and emboli. Uncontrolled intracranial hypertension can also lead to cerebral hemorrhage and infarctions. A small amount (10%) of postoperative neurological problems are related to CNS infections, and mostly they are opportunistic infections occurring as a result of immunosuppression. Most common pathogens are *Streptococcus pneumoniae, Hemophilus influenzae, Candida/Aspergillus* species and viral (herpes simplex, cytomegalovirus) agents. Immunosuppressive treatment can mask signs of infection (fever, leukocytosis, etc.), therefore, CNS infections should come into suspicion whenever there is alterations in neurological status. Central pontine myelinolysis syndrome is one of the most severe neurological complications that can occur following LT. It is pathologically characterized by symmetrical myelin loss at the pontine base, and it usually occurs as a result of rapid correction of chronic hyponatremia. Most common clinical symptoms are difficulty in swallowing/speech, confusion, convulsions and hypoventilation. There is no definitive treatment of central pontine myelinolysis, therefore it is very important to correct chronic hyponatremia slowly by monitoring serum sodium levels.[9,121-123]

INFECTIONS & PREVENTION

Infections are still among the most important causes of morbidity/mortality following LT. Long-term hospital stay prior to transplantation and impaired immunity precipitate recipient's colonization with resistant microorganisms. Early postoperative period has the greatest risk for infections due to intense immunosuppressive treatment; however, development of opportunistic infections during the first 48 hours in ICU is rare. The main reason for infections developing in the first postoperative week is the undetected infections that exist prior to transplantation. Signs of infection (fever, leukocytosis) can be masked depending on immunosuppression status, so that routine examination for cultures of blood, urine, tracheal secretions and others as required in the pre/postoperative period is recommended. Similar to the nosocomial infections observed in other surgical patients, wound site infections, pneumonia, peritonitis, cholangitis, urinary and central venous catheter-related infections, endocarditis, liver abscess, and *Clostridium difficile* colitis can be observed frequently within the first month. The most common infections among these are blood stream infections, pneumonia and abdominal/biliary infections.

Reported risk factors for bacterial infections at the early period include deceased donor, MELD score >20, hypoalbuminemia, intraoperative transfusion of more than 6 units of ES and 12 units of FFP, biliary-enteric anastomosis, long stay in ICU and at hospital, and re-operation. Infections at early period also include viral infections, mainly with cytomegalovirus and Epstein-Barr virus, and also with varicella zoster virus, human herpes virus-6 and adenovirus. Other than these, fungal infections can be seen in the rates of 5-42%, especially within the first two months. Infections caused by *Candida* are the most common ones, but opportunistic fungal infections that are highly mortal, such as aspergillosis, cryptococcosis and *Pneumocystis jirovecii* (*Pneumocystis carinii)* can also be seen. Risk of fungal infection increases during treatment of acute graft rejection using high dose corticosteroid and anti-lymphocytic agents (ATG-ALG). Reported risk factors for fungal infection following LT include preoperative renal dysfunction, basal fungal colonization, high MELD score, re-transplantation, massive transfusion, RRT requirement, prolonged ICU stay, human herpes virus-6 infection and re-intubation. Although fever detected in ICU following LT is mostly caused by infections, other causes have been reported in 13% of cases. Acute rejection should be considered first among extra-infectious causes; other causes can be drug-related fever, adrenal insufficiency, malignancies, transfusion-induced fever, fever secondary to surgical procedure; however, fever etiology cannot be identified in some cases. It should be noted that fever may not always develop in immunosuppressed patients, and sometimes even hypothermia can be observed.[2,4,6,10,55,124-130]

Main principles in the treatment of bacterial infections are as follows: early identification of the infectious agent (culture, antibiogram), control of the source (catheter withdrawal, wound debridement, abscess drainage, etc.) and prompt initiation of empirical antibiotherapy that covers flora in ICU. Meantime, immunosuppressive treatment dose can be lowered or discontinued as required. In viral infections, acyclovir (15-30 mg/kg/day) is used in the treatment of human herpes virus, and ganciclovir is used in the treatment of cytomegalovirus. In treatment of fungal infections, flucanozole can be used in *Candida* infections, amphotericin B and echinocandin group drugs (caspofungin, anidulafungin) can be used in *Aspergillus* infections. In many centers, echinocandin group drugs are preferred, due their advantages like not interacting with immunosuppressive drugs and not being nephrotoxic. Routine use of antifungal prophylaxis is still a subject of debate; there is no standard approach between different centers. However, it should be considered in patients who have high risk of fungal infections (re-operation, massive transfusion, RRT, biliary leak, etc.). Additionally, empirical antifungal treatment should be initiated along with wide-spectrum antibiotherapy in life-threatening conditions like resistant fever or septic shock. Serious infections developing after LT are associated with impaired graft healing, prolonged ICU stay and development of multi-organ failure. Management of septic shock is difficult due to underlying immunosuppression; it requires prompt application of many interventions described in treatment guidelines. It is important to plan the treatment while keeping interaction of anti-infective and immunosuppressive drugs and organ failures in mind; so that it is best to have an infectious disease specialist experienced in intensive care and transplantation infections within the team.[9,10,54,108,131]

Standard perioperative antibiotic prophylaxis can help to reduce infection risk following liver transplantation. Although there is not a standard antibiotic recommended for use in perioperative prophylaxis, 3rd generation cephalosporins (ceftriaxone, cefotaxime) are commonly used for this purpose. For prophylaxis of oropharyngeal candidiasis, nystatin solution is administered per orally. Preoperative application of inactive vaccinations, withdrawal of central venous and urinary catheters as soon as they are not required anymore, watching out for sterility while performing tracheal aspirations, prevention of RD by monitoring renal functions, obtaining samples for culture (tracheal secretions, urine, central catheter, rectal swab) regardless of whether there are signs of infection or not are some of the recommendations for prevention from infections. There are not sufficient evidence on effectiveness of applications as selective intestinal decontamination, oropharyngeal topical clorhexidine application, prebiotic/probiotic use and treatment with granulocyte colony stimulating factor (GCSF).[6,125,128,132,133]

POSTOPERATIVE NUTRITION THERAPY & GASTROINTESTINAL PROBLEMS

Disturbances of carbohydrate, lipid and protein metabolism are common in patients with ESLD. Levels of aromatic amino acids (phenylalanine, tyrosine, tryptophan) and methionine increase in blood while levels of branched chain amino acids (valine, leucine, isoleucine) decrease. Generally these patients also have malnutrition at the preoperative period. Malnutrition prior to liver transplantation has been reported to be associated with increased rates of postoperative infections, respiratory complications and prolonged ICU stay. In addition to malnutrition, factors such as stress due the major surgery, release of catabolic hormones and corticosteroid use necessitate nutritional support following LT. Since energy requirement increases moderately at the postoperative period, target calorie intake should be determined depending on the condition of the patient, as 25-40 kcal/kg/day. It should be initially started as 10-15 kcal/kg/day, and then gradually increased in stable patients to meet the the target calorie

in 5-7 days. In nutrition therapy, 50-60% of non-protein energy requirement should be provided by carbohydrates and 40-50% should be provided by lipids. As a result of increased protein catabolism, nitrogen loss increases; so protein requirement after LT should be calculated as 1.2-1.5 g/kg/day. Routine protein restriction in ESLD patients have been shown to have harmful effects, so protein restriction is only recommended in clinically severe cases of encephalopathy. Similarly, routine administration of proteins rich in branched chain amino acids has not been found to have any positive effects on morbidity/mortality, so they are only recommended to be used in patients with severe encephalopathy. Although many patients who do not have any complications following LT can start oral feeding, if the patient is not expected to have complete/adequate oral intake within 3 days, early enteral nutrition is recommended within the first 24 hours provided that gastrointestinal (GI) route is intact. Oral feeding should be started as soon as possible in patients who receive enteral nutrition through feeding catheter; however feeding catheter should not be withdrawn until sufficient oral intake (80% of the energy requirement) is provided. For cases in whom enteral nutrition is not applicable (Roux-en-Y anastomosis, ileus, etc.) or when target calorie intake can not be achieved by only enteral nutrition due to intolerance, parenteral nutrition can be administered. However, recent guidelines do not recommend initiation of parenteral nutrition during the postoperative first 5-7 days, so that, for cases in whom oral/enteral nutrition cannot be initiated following LT, glucose infusion sufficient to prevent hypoglycemia (2-3 g/kg/day) and fluid-electrolyte replacement should be administered at the early postoperative (first 5-7 days) period. Vitamins (B and C group) and micronutrients (especially zinc, phosphorus, magnesium) should be added to nutritional treatment, while monitoring blood levels if possible. Prevention of contamination and catheter-related infections are especially important for patients who receive parenteral nutrition.[10,134-138]

Gastrointestinal complications can be observed in approximately 50% of the LT patients. These complications can range from mild-moderate such as nausea-vomiting, diarrhea, dyspepsia, anorexia, abdominal pain, gastroesophageal reflux, constipation to life-threatening complications such as pancreatitis, colonic perforation, GI bleeding. Diarrhea is the most common among these, and anorexia and abdominal pain are the ones which affect daily activities most. Female sex, hiatal hernia prior to LT and re-hospitalization after LT have been reported as predisposing factors for GI complications. Gastrointestinal complications are usually caused by administered drugs (immunosuppressives, corticosteroids), infections (CMV, *Clostridium difficile*) and exacerbations of existing GI pathologies. Most of these complications can be managed via alterations in pharmacological and/or immunosuppressive treatments (dose reduction, discontinuation); however, complications like colonic perforation, persistent GI bleeding necessitate surgical intervention. Prophylactic measures against gastrointestinal complications include practices like restriction of corticosteroid administration, adjustment of the dose or discontinuation of immunosuppressive treatment depending on the symptoms (presents a risk for acute rejection), administration of H_2 receptor antagonists or proton pump inhibitors depending on risk state for stress ulcers prophylaxis. Timely diagnosis-treatment of these complications require radiological methods and endoscopic interventions.[139-143]

REJECTION

Acute cellular rejection is observed in approximately 20-30% of recipients following LT, which is less compared to the ratio in renal transplantation, and 5-10% of them progress to severe chronic ductopenic rejection that require retransplantation. Acute cellular rejection mostly occur 7-14 days (between 1-6 weeks) after LT; however, its manifestations can be observed earlier or later. Hyperacute graft rejection that develop within the first 7 days is rate in LT, and its etiology involves previously developed antibodies (ABO incompatible graft). Acute rejection is usually mediated by T-cells, and it causes injury in biliary tracts and vascular endothelium of the liver. Rejection is related with graft dysfunction and effects survival of graft adversely. Clinical/laboratory signs of rejection are non-specific and include fever, impaired graft function, elevation of plasma bilirubin and transaminase (AST, ALT) levels, coagulation test (INR, PT) abnormalities, thinning of the bile coming out from T-tube and its color getting lighter. Doppler USG and blood calcitonin level (infection, sepsis) provide guidance in differential diagnosis. In suspected cases, definitive diagnosis is made histologically by demonstration of areas of hemorrhagic necrosis in liver biopsy. Treatment depends on severity of rejection and the underlying diagnosis. Mild rejections can respond to increment of basal immunosuppressant dose, corticosteroid loading treatment, switching to mycophenolate mofetil and/or tacrolimus in patients receiving cyclosporine, whereas successive boluses of corticosteroids (methylprednisolone IV 1g/day, for 3 days) and/or anti-lymphocytic agents (ATG-ALG) are used in more severe conditions. Retransplantation may be rarely necessary in acute rejection.[1,6,10,55,141-144]

GRAFT DYSFUNCTION

Graft dysfunction is one of the most severe complications that may occur after LT.145 Various factors can predispose to graft dysfunction (Table 2).

Table 2: Factors related to graft dysfunction

Donor related	Procurement and Surgery related	Recipient related
• Donor age • Macrovesicular steatosis • High dose inotropic drug • Hypernatremia • Prolonged ICU stay • Graft weight/ Recipient weight ratio < 0.8% • Donation after cardiac death	• Prolonged cold ischemia time • Anhepatic phase time >100 min	• Impaired renal function • Elevated bilirubin level • Hemodialysis prior to transplantation • Low weight (BMI<18.5 kg/ m^2)

Initial Poor Function (IPF) / Primary Non-function (PNF)

Initial graft dysfunction following LT can be observed in a spectrum ranging from IPF that improves progressively to PNF that can require emergent retransplantation. Incidence of graft dysfunction varies between 2-14%; however, severe PNF is less than 5%. Although etiology is not clearly known, advanced donor age, prolonged cold ischemia time (>18 hours), steatotic liver graft, small graft size, severe reperfusion injury, uncorrected serious hyponatremia, prolonged pre/intraoperative hypotension, and long-term hospitalization of donor prior to organ removal have been reported as predisposing factors. Clinical and laboratory signs can be listed as follows: rapid elevation of liver transaminases (especially AST, >5000 U/L), jaundice, hypoglycemia, CNS alterations (confusion, coma), metabolic acidosis together with hyperlactatemia, hemodynamic instability, severe coagulopathy, oliguria and renal failure. Other PNF-resembling conditions such as hepatic artery thrombosis and other vascular problems, hyperacute rejection and severe infection (sepsis) should be ruled out in differential diagnosis (Table 3**)**. Definitive diagnosis is made after liver biopsy by demonstration of coagulation necrosis. The first step in its treatment is supportive treatment (transfusion of FFP, glucose infusion). Although some benefits of prostaglandin E1 infusion has been reported, its effectiveness has not been clearly determined. If there is no improvement of graft function within 24-36 hours, retransplantation should be performed before development of multi-organ failure. Until retransplantation, liver support systems (MARS, Prometheus®) can be used as bridging treatment to transplantation.[4,6,10,143,145-148]

Table 3: Differential diagnosis of graft dysfunction in intensive care unit

Initial Poor Function (IPF) / Primary Non-Function (PNF)
Preservation Injury
Rejection (*Hyperacute/Acute*)
Vascular Complications (*Hepatic Artery Thrombosis, Portal Vein Thrombosis, Caval Obstruction*)
Biliary Complications (*Biliary Leak, Stricture, Roux-en-Y Dysfunction, Papillary Stenosis)*
Drug-Related Hepatic Dysfunction
Infections

Table 4: Technical complications following liver transplantation and occurrence times

Complications	*Occurrence*
Abdominal Bleeding	
From anastomosis) site	Very early
From graft surface	Very early
Pseudoaneurysm	Early / late
Vascular Complications	
Hepatic artery thrombosis	Early
Hepatic artery stenosis	Late
Portal vein thrombosis	Early
Portal vein stenosis	Very early
Vena caval obstruction	Very early
Biliary Complications	
Biliary leak	Early
Biliary stricture	Late
Papillary stenosis	Early
Roux-en-Y dysfunction	Late
Non-specific surgical complications	
Intestinal obstruction	Early / late
Intraabdominal organ injury	Very early

Preservation Injury (Reperfusion Injury)

Preservation injury, also known as ischemia reperfusion injury, is an important cause of initial graft dysfunction, and it has a major effect on the course of LT. In solid organ transplantations, graft injury following reperfusion is responsible of delayed graft function or PNF in extreme cases. Donor risk factors related to preservation injury can be listed as advanced donor age (>60 years), macrovesicular steatosis, high dose vasopressor infusion, serious hypernatremia, donation after cardiac death, long-term ICU stay and prolonged cold ischemia time. Long anhepatic phase time in the recipient has also been found to be associated with preservation injury. Laboratory results indicate cholestasis (hyperbilirubinemia) that is characterized by elevation of transaminases at the acute period followed by elevation of alkalene phosphatase (ALP) and gamma-glutamyltransferase (GGT). Preservation injury should be considered when there is prolonged hyperbilirubinemia in patients who have risk factors. Ratio of acute cellular rejection of the graft increases in parallel with the severity of preservation injury; so that in cases where improvement is slow or when complete

clinical recovery cannot be achieved, liver biopsy should be performed for definitive diagnosis. Improvement is slower in patients who develop preservation injury following liver transplantation, and general supportive treatment should be continued. This condition generally recovers in 2-4 weeks; however, severe preservation injury can lead to increased morbidity/mortality and graft loss.[1,4,6,143,149]

EARLY COMPLICATIONS RELATED TO SURGICAL TECHNIQUE

Incidence of complications related to surgical technique following liver transplantation range between 5-10%. These complications mainly fall into four categories as abdominal bleedings, vascular complications, biliary complications and non-specific complications (Table 4). Treatment of these technical complications show a wide spectrum ranging from a simple surgical intervention (postoperative bleeding) to emergent retransplantation (hepatic artery thrombosis). The most common technical complications are bile leaks and strictures of biliary tract, followed by vascular complications. Attention of the intensive care team and close followup by the surgical team are of paramount importance in diagnosis and treatment of early surgical complications.[1,4,6,55,143]

CONCLUSION

Intensive care management of liver transplanted patients requires sophisticated monitoring and multi-disciplinary approach. Rapid hemodynamic stabilization, correction of severe coagulopathy, respiratory stabilization and early weaning from mechanical ventilation, appropriate fluid-electrolyte therapy, preservation of renal functions, prevention of graft rejection and prophylaxis/treatment of infection are particularly important in intensive care management of liver transplanted patients. Since early postoperative period is critical, close monitoring, stabilization and maintenance of cardiorespiratory functions, frequent examination of graft function, early identification of complications and prompt treatment of extrahepatic organ failure are mandatory in order to reduce mortality/morbidity.

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