Critical care of the liver transplant patient: an update
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The unique pathophysiology of patients with end-stage liver disease has important implications for their critical care treatment, particularly in the postoperative state. To gauge hemodynamic parameters and responses, each patient must be carefully evaluated for their place in the clinical spectrum of cirrhosis and portal hypertension. Although the data are limited, the biology of the consequences of liver disease is emphasized by novel treatments of hepatorenal syndrome, portopulmonary hypertension, and hepatopulmonary syndrome. These issues become more relevant with increased adult-to-adult living donor liver transplantation, in which technical considerations may further complicate the general treatment of the postoperative transplant patient. Curr Opin Crit Care 2002, 8:178–182 © 2002 Lippincott Williams & Wilkins, Inc.

Liver transplant patients are a unique clinical population, and the issues relevant to their ICU care reflect this fact. There is surprisingly little documentation of their care because they tend to be excluded from most studies based in the ICU.

Over the last few years, several concepts relevant to the critical care of the liver transplant patient have emerged. An improved understanding of the unique pathophysiology of the patient with end-stage liver disease (ESLD) has spurred novel treatments and approaches to the problems that emerge as they become critically ill or undergo orthotopic liver transplantation (OLT). To update and outline progress in the care of this patient population, the authors performed a Medline search using as keywords liver transplant, intensive care, critical care, outcomes, ventilation, hepatorenal, portopulmonary, cardiomyopathy, coronary artery, and prognosis. Relevant articles were culled, focusing on the period from October 2000 to November 2001 but including other recent articles of interest. This brief review emphasizes the biology and data behind emerging clinical issues.

Hemodynamic monitoring and responses
The postoperative treatment of the liver transplant patient is complicated by the profound physiologic derangements that accompany ESLD. Depending on the severity of ESLD, the patient will seek treatment with symptoms somewhere on a spectrum of progressive deterioration in hemodynamic, metabolic, cardiopulmonary, and nutritional status. Postoperative fluid and electrolyte management should be tailored to the individual patient, keeping in mind that the hyperdynamic state associated with liver disease makes the interpretation of hemodynamic parameters difficult.

One straightforward classification of disease severity in the postoperative liver transplant patient was recently suggested [1•]. In this schema, patients are assigned to one of four groups based on the presence and degree of a hyperdynamic circulation, low sodium level, malnutrition, portopulmonary hypertension, and cardiac dysfunction (Table 1). Although this classification has not been tested in clinical trials, it does provide a common sense framework for approaching the critical care management of the postoperative liver transplant patient. For example, a category I patient would be expected to have near-normal responses to fluid replacement and to require less fluid than a category II patient. The latter, having more chronic liver disease, will produce and lose...
more ascites and protein via the abdominal drain and require relatively aggressive management of fluid and protein losses. With a baseline increase in cardiac output and decrease in systemic vascular resistance, hemodynamic parameters may be difficult to interpret: the authors make the point that review of the operative record may reveal the hemodynamic parameter that most closely correlates with end organ function (such as urine output). Category III and IV patients generally have massive ascites and some degree of renal dysfunction. The approach to oliguria or hypotension must be more careful than for category I and II patients. Fluid and electrolyte management must be monitored for overly aggressive replacement of sodium and fluid, which can precipitate central pontine myelinolysis and cardiopulmonary compromise, respectively. Some degree of chronic hyponatremia should be tolerated, while guarding against the intravascular fluid overload that can overwhelm these patients’ fragile cardiopulmonary function.

This last point deserves emphasis, although intensive care management after OLT can involve massive amounts of intravenous fluid, these patients may not tolerate intravascular overload. A recent, retrospective review of 1,197 OLT patients found that the primary etiology for ICU readmission was cardiopulmonary dysfunction [2•]. On subgroup analysis, the basis for readmission was found to be fluid overload and lower inspiratory capacity. Because ICU readmission is associated with increased mortality, the authors suggested that a diligent treatment of intravascular overload should precede discharge from the ICU.

**Hepatorenal dysfunction**

Abnormal renal function is commonly found in the preoperative OLT patient and contributes both to ascites and metabolic abnormalities (particularly hyponatremia). To a large extent, a decrease in glomerular filtration rate reflects the response to compensated portal hypertension. In the early response, there is an increased plasma volume, increased cardiac output, a relatively normal arterial blood pressure, and decreased systemic vascular resistance. Importantly, the decrease in systemic vascular resistance is not systemic but is manifested principally in the splanchnic bed, with vasoconstriction in arterial beds elsewhere [3]. The marked vasodilation in the splanchnic bed leads to a decreased effective blood volume, with a progressive homeostatic activation of endogenous vasoconstrictive mechanisms (renin-angiotensin-aldosterone, sympathetic nervous system, endothelin-1). For reasons that are unclear, the splanchnic bed escapes this vasoconstrictive response; the kidneys do not.

Hepatorenal syndrome is the extreme manifestation of the renal response to portal hypertension and liver disease. Hepatorenal syndrome is present in 7 to 15% of cirrhotic patients in one of two forms. Type I is rapidly progressive, precipitated by a discrete event, and associated with a high and rapid mortality. In type II, there is a moderate but stable decrease in glomerular filtration rate [3]. Hepatorenal syndrome is usually reversible with OLT, although there may be a transient persistence of abnormal renal function postoperatively. After OLT, more than one third of patients require hemodialysis in the short term, and approximately 5% need chronic therapy [3]. Nephrotoxic drugs, in particular the immunosuppressants cyclosporine and FK506, should be avoided until renal function improves, generally 48 to 72 hours after OLT.

The central role of portal hypertension has important implications for the treatment of hepatorenal syndrome. Ultimately, the best treatment may be preventative, with aggressive treatment of any insult exacerbating the decreased effective blood volume resulting from ESLD. In patients with spontaneous bacterial peritonitis, a dose of intravenous albumin on diagnosis and 2 days later decreased the development of hepatorenal syndrome from 33% to 10% in a prospective, randomized trial [4]. Patients with established hepatorenal syndrome have been effectively treated with strategies directed at the splanchnic vascular congestion, which accompanies portal hypertension. Even after institution of hemodialysis, treatment of portal hypertension via insertion of a transjugular intrahepatic portosystemic stent-shunt improves renal function and mortality [5]. Intriguingly, administration of the vasopressin analogue terlipressin may improve hepatorenal syndrome by virtue of splanchnic vasocostriction. This approach stands in marked contrast to the traditional use of renal vasodilators, such as renal-dose dopamine and prostaglandins, which has never had a consistently positive effect. A recent study treated 12 patients with type I hepatorenal syndrome with 1 week of intravenous terlipressin (2 mg twice daily) in addition

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**Table 1. Proposed classification of end-stage liver disease severity for the purposes of ICU management**

<table>
<thead>
<tr>
<th>Category</th>
<th>Hyperdynamic circulation (elevated cardiac output)</th>
<th>Low plasma sodium</th>
<th>Malnutrition (low albumin)</th>
<th>Portopulmonary hypertension</th>
<th>Cardiac dysfunction (preoperative echo, dobutamine stress echo)</th>
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Adapted with permission [1•].

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to albumin. Renal function improved, with creatinine decreasing by almost half and median urinary sodium increasing from 7 to 38 mEq/L [6••]. Three patients were transplanted after treatment, but nine died, indicating that this therapy may be most useful as a bridge to OLT.

**Portopulmonary hypertension and hepatopulmonary syndrome**

The pulmonary manifestations of ESLD are not uniform but can be dramatic. Portopulmonary hypertension is present in 5 to 10% of patients seeking liver transplant evaluation [7]. Its pathogenesis involves both vasoconstriction and thrombosis. Portopulmonary hypertension is defined by portal hypertension in combination with a mean pulmonary arterial pressure greater than 25 mm Hg with no evidence of left heart failure ($P_{CWP} < 15$ mm Hg). The condition is designated severe when mean pulmonary arterial pressure exceeds 45 mm Hg, at which point the mortality of OLT approaches 100% [7]. In contrast with the vasoconstrictive portopulmonary hypertension, hepatopulmonary syndrome is characterized by pulmonary vasodilation. Occurring in 8 to 15% of cirrhotic patients, hepatopulmonary syndrome is defined by hypoxemia, the demonstration of right-to-left shunting (contrast echocardiography), an increased alveolar-arterial oxygen gradient, and absence of intrinsic cardiopulmonary disease [8,9••]. Unlike portopulmonary hypertension, hepatopulmonary syndrome tends to prompt OLT because transplantation is its only effective therapy [8].

In both portopulmonary hypertension and hepatopulmonary syndrome, the pulmonary vasculature seems to be affected by vasoactive mediators released into the splanchnic circulation. These escape hepatic metabolism because of liver disease or are shunted into the systemic circulation as a result of portal hypertension [10], Why a particular syndrome develops is unclear, but development is probably the result of individual patient responses, predispositions, and environmental factors. For example, both nitric oxide and endothelin-1 have been suggested to be important to pulmonary vasodilation [9••,10], whereas hepatopulmonary syndrome may be more common at lower altitudes [11].

Recent small or anecdotal reports have suggested that both portopulmonary hypertension and hepatopulmonary syndrome can occasionally be ameliorated by medical treatments. In portopulmonary hypertension, continuous intravenous infusion of prostaglandin I$_2$ can decrease mean pulmonary arterial pressure to the point that the risk of OLT becomes acceptable [12,13]. The treatment must be continued during the operation and postoperatively for many months. The safety of this approach remains to be determined: six of 10 patients from the Mayo series died while on infusion therapy, three from progressive portal hypertension with stable pulmonary hemodynamics [13]. In theory, long-term exposure to prostaglandin I$_2$ may worsen portal while improving pulmonary hypertension [12,13]. Intravenous administration of methylene blue, a potent guanylate cyclase inhibitor intended to decrease the vasodilatory effect of nitric oxide, temporarily increased partial pressure of oxygen in arterial blood ($P_{O_2}$), pulmonary vascular resistance, and systemic vascular resistance in seven patients with severe hepatopulmonary syndrome [9••]. The magnitude of the effect was variable among individual patients, and a subsequent case report found no benefit to methylene blue administration [14]. Although these novel medical treatments require further study before firm conclusions are made about utility, they illustrate the potential reversibility of the pathologic consequences of liver disease.

**Ventilation and pulmonary edema**

The liver transplant patient does not tolerate respiratory compromise well. Already immunocompromised because of ESLD, Kupffer cell dysfunction, or posttransplant immunosuppression, endotracheal intubation and ICU readmission promote infection and mortality. In a randomized, prospective study from Italy, 40 solid organ transplant (liver, renal, lung) patients with acute respiratory failure (respiratory rate > 35 bpm, $P_{O_2}$/fraction of inspired oxygen [$F_{I_O_2}$] < 200, accessory muscle use) received either supplemental oxygen therapy or positive pressure ventilation by face mask [15]. All patients underwent phsyotherapy and incentive spirometry. The ventilation group had fewer intubations (4 of 20 vs 10 of 20), a shorter ICU stay (5.5 vs 9 d), and a trend toward decreased hospital mortality (7 of 20 vs 11 of 20). Because many centers can manage positive pressure ventilation outside the ICU, this study suggests that a more aggressive approach to the transplant patient who is developing respiratory failure may obviate the need for ICU admission altogether. While in the ICU, face mask ventilation may allow the liver transplant patient to remain nonintubated while fluid overload is dealt with.

Fluid overload and cardigenic failure are not the only causes of pulmonary edema in the OLT patient, especially perioperatively. Reperfusion of the donor liver during the transplant operation, when combined with transfusion of blood products, is associated with a brief but potentially severe form of lung injury. A recent study of seven patients collected endotracheal fluid within 15 minutes of the development of acute pulmonary edema perioperatively [16•]. No patient had hemodynamic parameters consistent with a cardiogenic etiology. The fluid had the characteristics of an exudate in six of the patients. All instances of pulmonary edema arose postreperfusion (usually within 1–2 h), were generally associated with substantial amounts of blood products, and were transient in nature, resolving after several hours. An eighth patient who developed pulmonary edema 60 minutes after reperfusion died intraopera-
tively, and on autopsy was found to have died from fat embolization to the lung after reperfusion of a graft with a high fat content. Although the authors suggested that transfusion-related acute lung injury was the cause of pulmonary edema, the fact that it arose postreperfusion and could be associated with fat embolization raises the possibility of a multifactorial injury precipitated by reperfusion.

The heart and the liver transplant patient
Two issues should be highlighted about the heart and the critical care of the OLT patient.

Cirrhotic cardiomyopathy
Patients with cirrhosis tend to have impaired ventricular contractility in response to physiologic stress or pharmacologic stimulation. In patients evaluated at rest, those with cirrhosis with ascites had enlargement of both atria and the right ventricle and evidence of mild diastolic dysfunction when compared with normal controls or patients with cirrhosis without ascites [17]. Why portal hypertension can lead to cardiac dysfunction is unclear but may reflect both mechanical influences (increased intra-abdominal pressure affecting intrathoracic pressure) and the effects of systemic increases in vasoactive substances (nitric oxide, endothelin-1) [17,18]. Animal models suggest alterations in the expression and signaling of the cardiac β-adrenergic receptor [18]. Treatment is empirical, but impaired contractility may explain a lack of response to dobutamine after OLT.

Coronary artery disease and liver transplantation
The incidence of significant coronary artery disease in patients being evaluated for liver transplantation is likely 5 to 10%, and portends a poor prognosis after liver transplantation, even with treatment [19]. Active coronary artery disease is a relative contraindication to liver transplantation and at a minimum should be treated as aggressively as possible preoperatively (stenting, angioplasty). The success of liver transplantation has forced programs to reconsider how best to manage coronary artery disease, and there are reports of simultaneous cardiac bypass and OLT [20].

Living donor liver transplantation
Adult-to-adult living donor liver transplantation has become more prevalent and will likely increase in the next few years. Several issues relevant to the critical care of right lobe liver transplant patients should be highlighted.

(1) There is a significant incidence of biliary tract complications (leak or stricture) after right lobe living donor liver transplantation, in the range of 28 to 34% [21,22,23••]. This incidence carries a significant risk of reoperation and possibly of infection and sepsis.

(2) The right lobe graft is very susceptible to congestion, either from too much inflow (portal venous hypertension) or from outflow obstruction (hepatic venous anastomosis, inadequate preservation of intrahepatic venous collaterals). Retransplantation may be required to address the resulting hepatocytic destruction or graft dysfunction [22,23••]. It is generally accepted that a minimum graft size to recipient size ratio of greater than 0.8% is necessary to provide adequate liver volume; however, graft congestion can precipitate a “small for size” syndrome, even with a relatively large graft.

(3) The arterial anastomosis is generally performed between smaller vessels than in a routine cadaveric operation. The risk of hepatic artery thrombosis may be higher and should be actively searched for with routine and early postoperative Doppler examinations.

(4) To date, most of the North American experience has been with relatively healthy recipients [21,23••]. The problems noted here are to some extent a function of the learning curve associated with a difficult operation, which may be exacerbated when the operation involves patients who are more ill.

In brief, the critical care of the right lobe liver transplant recipient should include aggressive monitoring for and treatment of signs of sepsis or bile leak, careful evaluation of liver function and hepatic artery patency with biochemical tests and frequent Doppler examinations, and recognition of the “small for size” syndrome with exacerbations of coagulation defects, ascites, sepsis, renal function, central nervous system status, and hemodynamics.

Conclusions
The critical care of liver transplant patients needs to be individualized to the specific pathophysiology manifested by the patient. Patients should be assessed for their place on the spectrum of clinical disorders associated with ESLD, with particular attention to renal, pulmonary, and cardiac function. In addition, the patient who has undergone right lobe living donor liver transplantation is at risk for biliary complications, hepatic arterial thrombosis, sepsis, and “small for size” syndrome. Further studies are needed to clarify the best means of approaching the potentially reversible physiologic defects that result from end-stage cirrhosis.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
** Of outstanding interest
A thorough overview of critical care topics and their relation to the liver transplant patient, of particular value for a useful classification of disease severity in this patient population.


This retrospective study convincingly argues for a careful approach to the fluid management of the liver transplant patient.


An interesting study that supports the notion that splanchic vasodilation is central to the pathogenesis of renal dysfunction in the patient with portal hypertension.


A well-written report, and the largest published series to date of right lobe living donor liver transplantations performed in North America. Technical issues are thoughtfully addressed.