Acute-on-Chronic Liver Failure in Cirrhosis: Defining and Managing Organ Dysfunction

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Introduction

The term 'acute-on-chronic liver failure' was first used in the 1960s mainly in relation to flares of viral hepatitis. It was not until the turn of the millennium, however, that the term entered the everyday vocabulary of hepatologists when it was used to describe the pathophysiological deterioration in patients with cirrhosis mainly in the context of trials utilizing liver support devices [1]. Since then, a consensus definition of acute-on-chronic liver failure has been fiercely debated. The terms 'compensated' and 'decompensated' liver disease are rarely used in the critical care arena with patients being defined with regard to the degree of organ dysfunction rather than by quantifying liver synthetic function *per se*. Moreover, it has been shown that the prognosis in patients with cirrhosis is strongly correlated with the number of failing organs [2–4] and that certain cohorts of patients with severe hepatic encephalopathy, acute variceal bleeding, and organ failure benefit from admission to a critical care environment [5].

In this chapter, we define acute-on-chronic liver failure as it is normally used and suggest an alternative definition of liver failure requiring critical care and organ support. Furthermore, we will describe the common precipitants and therapeutic modalities, concentrating on critically ill patients with cirrhosis.

Defining Acute-on-Chronic Liver Failure

To hepatologists, acute-on-chronic liver failure encompasses patients with cirrhosis in whom a precipitating factor or triggering event such as infection or acute variceal bleeding results in an acute pathophysiologic deterioration with progressive organ dysfunction. In some patients the precipitant is overt, while in others it remains elusive. The acute deterioration is typically characterized by a hyperdynamic circulation, low systemic vascular resistance, renal dysfunction, worsening portal hypertension and hepatic encephalopathy. These patients have striking similarities with other critically ill patient groups [6] and early aggressive management and organ-targeted goal-directed therapies may prevent progression to irreversible organ failure and death [7].

Quantifying Organ Dysfunction in Cirrhosis

Figure 1 encapsulates the major organ systems which are affected to one degree or another in patients with cirrhosis. It is particularly important to factor in the significant effects of liver dysfunction on the immune system, adrenals, gut, and portal circulation. Although it has not been examined in depth it is likely that 'septic liver dysfunction' will have many of the phenotypical characteristics that are seen in 'decompensated' chronic liver disease. It may indeed be that low-grade portal hypertension and its complications may be present and relevant to the patient with 'septic' liver dysfunction.

The admission to an intensive care unit (ICU) environment will encompass patients with recognized chronic liver disease and its associated complications. In addition however, we must consider those with disease processes who are not normally considered to have pre-existing liver disease. One of the largest such groups are those with non-alcoholic fatty liver disease, a rapidly growing cohort of patients in the general population. These individuals will not be recognized as having 'preceding liver disease'. This is a group of patients whose livers are highly susceptible to oxidative stress, have pre-existing insulin resistance, and who will develop 'stiff' livers with early development of cholestasis and ascites.

Another cohort of patients who frequently develop liver dysfunction are those undergoing liver resection. Many of these patients will have received preoperative chemotherapy and will have significant fatty livers. Removal of a significant amount

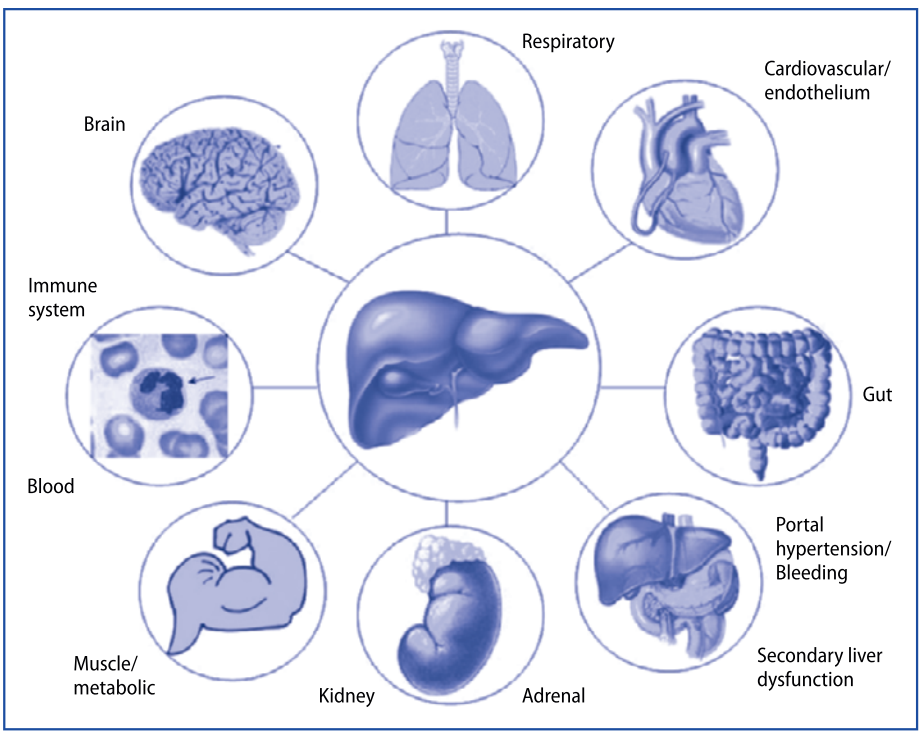

Fig. 1. A pictorial representation of the major organ systems that are affected in patients with cirrhosis.

of liver with a fatty baseline will result in a markedly reduced 'functional' residual volume. Such patients will then develop many of the features of 'small for size' syndrome with cholestasis and portal hypertension. It may be that many of the features of end organ dysfunction such as portal hypertension, gut edema and congestion, renal vasoconstriction, portal shunting and hepatic encephalopathy may be seen at 'low titer' in those with so called 'septic liver cholestasis'.

Physiological derangement can be numerically quantified using a variety of scoring tools including the Acute Physiology and Chronic Health Evaluation (APACHE) [2, 8] and Sequential Organ Failure Assessment Score (SOFA) [9]. These scores have been validated to predict survival in general ICU populations but have been examined to a lesser extent in patients with cirrhosis (reviewed in [10]). Specific scoring systems for cirrhosis, such as the Child-Pugh-Turcotte system [11] and Model of End-stage Liver Disease (MELD) [12] have not been examined to any significant degree in critical care environments. More recently the RIFLE (Risk of renal failure, Injury to the kidney, Failure of kidney function and End-stage renal failure) classification was shown to demonstrate high discriminative power as an independent variable along with a SOFA score of ≥ 9 in predicting hospital mortality in critically ill patients with cirrhosis [13]. The outcome of patients with cirrhosis admitted to ICU and the utility of the various organ scoring systems in relation to predicting survival is reviewed in [10] and will not be the subject of this chapter. Instead we will focus on an evidence-based approach to the management of organ dysfunction in cirrhosis.

It should perhaps be considered that the definitions of acute-on-chronic liver failure (**Table 1**) may require adaptation for patients with liver disease in the critical environ. There already exists in the hepatology world considerable discussion as to the definition and distinction of 'decompensated' liver disease and acute-on-chronic liver failure. Many of the patients described with these syndromes are managed in a ward or even outpatient environment. The more severe end of the spectrum of organ dysfunction, with associated liver failure is not adequately described by the existing definitions. We would suggest that the term 'liver failure requiring critical care and organ support' (**Table 1**) could be adopted to encompass a number of subgroups, which would envelop the disease spectra that are encountered on a daily basis in the ICU. The subgroups and suggested features are summarized in **Table 1**.

Pathogenesis

It is generally well recognized that the development of organ dysfunction in cirrhosis can be triggered in several different ways characterized by a 'second hit' in a patient with pre-existing chronic liver disease. Of all of these precipitants, infection, and the resultant systemic inflammatory response syndrome (SIRS), is perhaps the most important and most prevalent within this population. Patients with cirrhosis are functionally immunosuppressed and prone to infection [14]. Sepsis and/or SIRS occur in approximately 40 % of hospitalized patients with cirrhosis and the resultant organ failure is a major cause of death [15]. Specifically, the interplay between infection/inflammation and the development of hepatic encephalopathy has become well recognized and one of the ongoing challenges will be the separation of inflammation from infection. Similar functional immunosuppression can be seen in patients with acute liver function [16].

An ammonia load resulting from upper gastrointestinal bleeding or following the formation of a portocaval shunt or TIPS (transjugular intrahepatic portosystemic

Table 1. Definitions

1. **Liver failure not requiring organ support (incorporating acute-on-chronic liver failure/ 'decompensated' cirrhosis)**
   The development of ascites, hyperbilirubinemia, renal dysfunction, grade 1/2 hepatic encephalopathy in a patient with pre-existing cirrhosis
2. **Liver failure requiring critical care and organ support**
   The term encompasses the following 3 groups:
   1. The critically ill patient with cirrhosis [Point 3]
   2. Liver dysfunction in association with critical illness [Point 4]
   3. Acute liver failure [Point 5]
3. **The critically ill patient with cirrhosis**
   Pre-existing cirrhosis in association with one of more of the following:
   - Major variceal hemorrhage requiring airway management
   - Severe hepatic encephalopathy (grade 3/4)
   - Acute renal dysfunction requiring renal replacement therapy
   - Hypotension (requiring fluids and vasopressors)
   - Intra-abdominal hypertension with end-organ dysfunction
   - Metabolic acidosis
4. **Acute liver dysfunction in association with critical illness**
   The term encompasses the following 3 groups:
   1. Septic cholestasis
   2. 'Small for size' syndrome post-liver resection (ascites, portal hypertension, cholestasis +/– hepatic encephalopathy)
   3. Liver trauma
5. **Acute liver failure with organ dysfunction**
   Acute liver dysfunction (with no pre-exisiting liver disease) in association with any of the following:
   - Coagulopathy
   - Hepatic encephalopathy
   - Metabolic acidosis
   - Renal dysfunction
   - Cardiovascular failure
   - Respiratory failure

shunt) can lead to the development of hepatic encephalopathy [17] or the resultant change in systemic and splanchnic hemodynamics can precipitate right heart dysfunction [18].

It is important to recognize that the development of organ dysfunction is likely to be observed as a down-stream occurrence following an inflammatory event, with patients moving from a chronic stable phenotype to that of organ dysfunction and critical illness (**Fig. 2**). Other precipitants resulting in clinical deterioration, such as new onset portal vein thrombosis, hepatocellular carcinoma, use of non steroidal anti-inflammatory drugs, over use of diuretics, and use of sedatives should also be considered. One of the major challenges in the management of this cohort of critically ill patients with cirrhosis is the separation of those with reversible organ dysfunction in association with a precipitant and those where the deterioration is that of inexorable decline in association with end-stage liver disease.

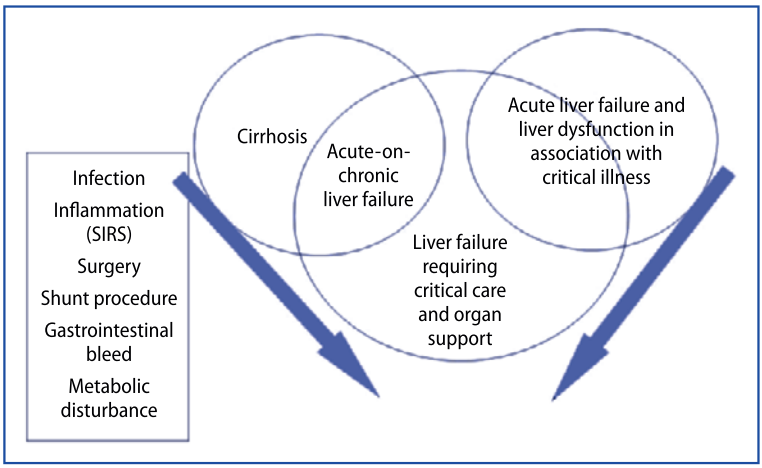

Fig. 2. A diagrammatic representation of the relationship between acute liver failure, liver dysfunction in association with critical illness and the patient with cirrhosis, and the development of liver failure requiring critical care and organ support. Factors such as infection and inflammation (systemic inflammatory response syndrome [SIRS]) can precipitate the development of multiorgan dysfunction.

Associated Organ Dysfunction

Adrenal

A number of studies have shown that relative adrenal insufficiency (defined as an impaired adrenal response to adrenocorticotropic hormone (ACTH) is common in critically ill patients with cirrhosis and its incidence correlates with the severity of liver disease (Child-Pugh and MELD scores) in addition to physiological derangements (APACHE II and SOFA scores) [19]. These authors [19] also noted a significantly increased mortality in patients with impaired adrenal response compared to those without. This phenomenon can exist in the absence of sepsis and led one group to propose the term 'hepatoadrenal syndrome'; this group also noted a relationship with cholesterol levels [20]. The effect of treating patients with cirrhosis and septic shock with low dose hydrocortisone has been evaluated prospectively in a small study [21]. Relative adrenal insufficiency was diagnosed in 68 % of patients and this group was treated with hydrocortisone. Treated patients had a quicker resolution of shock and an apparent survival benefit compared to historical controls that had not undergone adrenal function testing. A similar incidence is seen in patients with acute liver failure [19].

Brain

Hepatic encephalopathy remains a major clinical problem in patients with cirrhosis and when hepatic encephaolopathy is severe in cirrhosis, patients may develop varying degrees of confusion and coma [22]. In patients with severe liver dysfunction and, therefore, impaired urea synthesis, glutamine is synthesized from ammonia and glutamate and acts as a major alternative ammonia detoxification pathway. Glutamine synthesis occurs within astrocytes and may be one of the main causes of brain swelling. Clinically significant brain swelling and increased intracranial pres-

sure (ICP) are effectively only seen in acute liver failure. More recent studies have suggested that intracranial hypertension is less frequent than previously described, being seen in 25 % of acute and hyperacute etiologies but in only 9 % of those with subacute liver failure. Magnetic resonance imaging (MRI) studies in liver cirrhosis have shown evidence of astrocyte swelling in patients with cirrhosis, with the degree of abnormality correlating with neuropsychological function and normalizing after liver transplantation [23]. In rare circumstances, clinically significant brain swelling may be seen; this should be considered especially when patients are exposed to a TIPS shunt without prior exposure to hyperammonemia [17].

To date, current therapies for hepatic encephalopathy have been based upon ammonia lowering strategies based on the hypothesis that the colon is the primary organ responsible for the generation of ammonia. Therefore, the mainstay of current therapy of hepatic encephalopathy has been the administration of non-absorbable antibiotics, lactulose, and protein restricted diets. However, the results of two recently published studies [24, 25] suggest that the colon may not be the only focus for ammonia reduction suggesting that the role of other organs in ammonia metabolism needs to be explored. In a recently published systematic review of 22 randomized trials using lactulose/lactitol and non-absorbable antibiotics for hepatic encephalopathy, it was concluded that there is 'insufficient' evidence at present to recommend or refute their use in hepatic encephalopathy [24]. Compared with placebo or no intervention, lactulose/lactitol had no significant effect on mortality.

Historically, protein restriction for the treatment of hepatic encephalopathy has been advocated based on anecdotal observations. This is in direct opposition to the fact that in cirrhosis, higher protein intakes are required to maintain a positive nitrogen balance. A recent small randomized study in cirrhotic patients with hepatic encephalopathy demonstrated that diets with a normal protein content can be administered safely and without detrimental effect on resolution of encephalopathy [25].

The most important management principal in patients with grade 3/4 hepatic encephalopathy is care of the airway. Patients with cirrhosis and hepatic encephalopathy alone should have a good prognosis providing the airway is protected against aspiration and that secondary chest sepsis is avoided.

Although we know that ammonia is important in the pathogenesis of hepatic encephalopathy, clinical observations do not always show a consistent correlation between the concentration of ammonia in the blood and the symptoms of hepatic encephalopathy. Therefore, it is probable that other factors, in addition to hyperammonemia, are important in modulating the effects of hyperammonemia. Recently the role of inflammation on the development of hepatic encephalopathy has been highlighted. Sepsis/inflammation is a frequent precipitant of hepatic encephalopathy and studies have suggested rapid progression in the severity of hepatic encephalopathy in those patients with acute liver failure who have more marked inflammation [26]. These observations have been confirmed in cirrhotic patients [27]. Altering the gut flora and gut permeability may justify the use of probiotic therapy, however, further work is required before this can be considered as standard therapy [28]. The role of beta-blockers, well recognized in the stable patient to decrease portal hypertensive enteropathy and thus 'gut leak', should be considered in the critical care setting if hemodynamics allow.

The use of a 'detoxification device' in liver failure might lead to a temporary improvement in the patient's condition, allowing the liver to recover spontaneously. Liver support systems, such as MARS (molecular adsorbents recirculating system),

may have a role and has been found to be of benefit in improving hepatic encephalopathy grade in patients with acute-on-chronic liver failure independently of changes in ammonia and cytokines. A recent study looking at MARS showed improved resolution of hepatic encephalopathy but did not demonstrate any survival benefit; although the study was not powered for survival [29]. In the meantime, current guidelines will need to be revised with strict attention being paid to treating the precipitating factors, correction of dehydration, electrolyte and acid-base imbalance, constipation, and infection.

The management of hepatic encephalopathy in association with acute liver failure requires a different management protocol. The development of grade 3/4 hepatic encephalopathy is associated with a worse prognosis and more importantly may be complicated by the development of cerebral edema and raised ICP. Management is similar to that of neurocritical care although these cohorts of patients frequently do not autoregulate to pressure and increasing blood pressure without access to ICP monitoring is inadvisable. Fever and a SIRS-type response are associated with increased risk of elevated ICP and should be avoided. The use of hypothermia is being examined in a randomized controlled trial. The ICU management of acute liver failure requires a multidisciplinary approach in a center offering emergency liver transplantation [30].

Blood (Coagulopathy)

Patients with cirrhosis are invariably coagulopathic, resulting from a combination of poor liver synthetic function impairing the ability to produce clotting factors and fibrinogen, and thrombocytopenia. Platelets, fresh frozen plasma, and cryoprecipitate frequently need to be infused in the context of invasive procedures and variceal bleeding. It is also important to consider immune mediated thrombocytopenia and heparin-induced thrombocytopenia in addition to hypersplenism in those patients with thrombocytopenia. Standard measures of coagulation may be inadequate and the role of thromboelastography in the monitoring and management of patients with cirrhosis in the ICU can be invaluable [31, 32]. Thromboelastography provides a global assessment of hemostatic function from initial clot formation to clot dissolution. Prothrombotic states are not uncommon in liver disease and may not be adequately recognized using standard clotting profiles but can be characterized by thromboelastography. Such patients may be at increased risk of venous thrombosis (including portal vein) and embolic disease.

Cardiovascular

Cardiac and vascular dysfunction is common in cirrhosis but often underestimated. The presence of a hyperdynamic circulation in patients with cirrhosis and portal hypertension is well established, manifesting as high cardiac output, a hyporesponsive peripheral circulation, low systemic vascular resistance, and increased portosystemic shunting [33]. These phenomena may be secondary to a reduction in vascular responsiveness and desensitization to vasoconstrictors (endothelin I, angiotensin II and sympathomimetics) or to the effects of vasodilators (nitric oxide and prostacyclins) with resultant vasodilatation. These hemodynamic changes are responsible for many of the complications of cirrhosis we see including variceal bleeding, recurrent ascites and hepatorenal syndrome. Despite having an increased circulating blood volume, patients with cirrhosis are centrally volume deplete prior to the

development of an acute insult. As such, they have limited reserve to accommodate further vasodilatation and hypotension and are inevitably profoundly volume depleted with the additional insult of sepsis or variceal hemorrhage. The cornerstone of management is thus early and aggressive volume repletion despite the presence of peripheral edema and ascites. Salt restriction in critically ill patients with cirrhosis is not required. The presence of cirrhotic cardiomyopathy and diastolic dysfunction may further complicate matters [34] and thus optimal volume repletion may be difficult to ascertain. Invasive monitoring is, therefore, frequently indicated. Dynamic hemodynamic monitoring as opposed to static cardiac measurements may be a better indication of volume responsiveness particularly in the context of diastolic dysfunction.

Portopulmonary syndrome (the development of pulmonary hypertension in a patient with portal hypertension resulting from intense vasoconstriction of pulmonary capillaries and pulmonary vascular remodeling) should always be considered and may be screened for using echocardiography. If present, a pulmonary flotation catheter may be placed in order to monitor therapies administered to decrease pulmonary hypertension such as sidenafil or prostacyclin.

If volume repletion is inadequate as a first line therapy then vasopressors should be instituted using norepinephrine in the first instance. Recently there has been a vogue for introduction of low dose vasopressin as an adjunct to catecholamines in refractory septic shock. A recent multicenter randomized double blind trial did not show a survival benefit [35] but this does not rule out a role for vasopressin in those patients who have high requirements for catecholamines. In patients with sepsis and vasopressor-dependent shock, international guidelines recommend the use of steroids although this remains an area of controversy. Initial studies were very positive with improved outcome [36] whilst a recent large multicenter study could not demonstrate any survival benefit.

Gut/nutrition

The gastrointestinal tract is often a neglected organ in patients with cirrhosis. It is important to remember that the small intestine provides a significant contribution to ammonia generation (along with the kidney), that it contributes significantly to endotoxemia through decreased integrity of the bowel wall leading to bacterial translocation, that portal hypertensive enteropathy causes malabsorption and chronic blood loss, and the implications of significantly raised intra-abdominal pressure from the accumulation of ascites. Moreover, adequate nutrition with appropriate supplementation of vitamins and trace elements is perhaps one of the most important therapies that can be given to patients with alcoholic hepatitis and acute-on-chronic liver failure who are invariably malnourished with little muscle mass and are in a catabolic state. The most appropriate type and nature of nutrition has yet to be established in prospective trials.

Intra-abdominal pressure can be measured through a nasogastric tube or via the urinary catheter. Intra-abdominal hypertension is deleterious to cardiovascular, respiratory and renal function [37] and can be reduced effectively by judicious low volume (4–6 liters) paracentesis.

Immune System

Patients with cirrhosis are particularly prone to infection which is frequently a precipitant of hepatic encephalopathy, renal failure, and circulatory collapse. Bacterial infections are of particular concern in patients with cirrhosis because they are poorly tolerated [15]. The increased risk of infection is secondary to impairment of several host defense mechanisms including impaired neutrophil function [38]. The hemodynamic derangement of cirrhosis resembles that produced by endotoxin, and bacteremia can greatly exacerbate this state, producing hypotension, hepatorenal syndrome, deterioration in mental status, and increased portal hypertension with risk of variceal bleeding. Factors that predispose to bacterial infection include malnutrition with impaired cell-mediated immunity, decreased integrity of the bowel wall leading to bacterial translocation, and impaired phagocytic activity of the hepatic and splenic reticuloendothelial system resulting from portal hypertension. Tuftsin, a natural tetrapeptide known to stimulate phagocytosis by neutrophils, has also been shown to be reduced in cirrhosis [39]. Neutrophils from patients with superimposed acute alcoholic hepatitis have depressed phagocytosis, intracellular killing and metabolic activity, although they have a greater capacity for ingestion and killing of bacteria than neutrophils of patients with cirrhosis alone [38]. Neutrophil dysfunction with high resting oxidative burst and reduced phagocytic capacity is present in patients with cirrhosis and alcoholic hepatitis and has been associated with a significantly greater risk of infection, organ failure and mortality [40]. Neutrophil phagocytosis was also found to be significantly impaired just 4 hours after inducing hyperammonemia in patients with stable cirrhosis given an amino acid solution but not in those given a placebo solution and it is possible that ammonia may, in part, account for the increased susceptibility to infection found in patients with liver disease [41]. Hyponatremia was also shown to impair phagocytosis and, when combined with ammonia, these effects were additive supporting the clinical observation in patients with cirrhosis, that hyponatremia is associated with an increased risk of infection [42].

Muscle/metabolic

Muscle plays an important role as an ammonia removing organ and in a hyperammonemic state, muscle detoxifies ammonia through conversion to glutamine [43]. Therefore, malnourished cachectic patients with low muscle mass have less capacity to detoxify ammonia putting them at greater risk for the development of hepatic encephalopathy, particularly during episodes of sepsis. Metabolic disarray is often caused by dehydration, diarrhea and over-diuresis. Strict attention needs to be paid to correcting these factors. Renal replacement therapy may be indicated in the absence of renal impairment to correct hyperlactemia, acid-base disturbances, hyperammonemia and hyponatremia with caution not to raise blood sodium levels too quickly.

Portal Hypertension/variceal Bleeding

Acute variceal bleeding is now associated with markedly improved survival but it can be extremely challenging to manage patients with bleeding, organ dysfunction and hepatic encephalopathy in a ward environment, and these patients frequently require, and indeed benefit from, augmented levels of care in high dependency and

intensive care environments. It is no longer acceptable to battle with agitated, hemodynamically unstable patients with variceal bleeding in the endoscopy suite without the presence of an anesthetist and/or airway protection by way of intubation and performed in an operating room or intensive care facility. Timely endoscopic therapies, including variceal band ligation and histoacryl glue injection, following aggressive resuscitation and correction of clotting abnormalities have been shown to be associated with favorable outcomes in patients with cirrhosis. Patients warrant ICU admission when the bleeding is uncontrolled, the patient is at risk of aspiration, and during periods of hemodynamic instability. Frequently, infection is a precipitant for variceal bleeding and the administration of empirical broad spectrum antibiotics is recommended, particularly when patients are at risk of aspiration pneumonia. The long-acting vasopressin analog, terlipressin, has immediate splanchnic vasoconstrictor action and has been shown in several placebo-controlled trials to reduce failure to control bleeding and to improve survival [44]. Its use is warranted early on during resuscitation before diagnostic endoscopy and administration is recommended every 4 to 6 hours for 2 to 5 days. Measurement of portal pressure is increasingly being used to guide the prescription of secondary prophylactic pharmacotherapy against re-bleeding such as non-specific beta-blockers or nitrates. Rescue therapy for uncontrolled variceal bleeding may warrant TIPS or portocaval shunt surgery. Indeed use of portal pressure measurement may delineate a high-risk group of patients (hepatic venous wedge pressure was > 20 mmHg) who should be considered for early intervention [45]. The most recent evidence-based guidelines for the management of acute variceal bleeding and portal hypertension were published in the consensus proceedings of Baveno IV [46].

Renal

Oligoanuria and renal dysfunction are very common in the critically ill patient with cirrhosis and the development of renal failure confers a poor prognosis particularly in the context of sepsis and the development of multiorgan failure [2–5]. Renal dysfunction is often labeled as 'hepatorenal syndrome' when in actual fact other causes of renal failure (particularly pre-renal) are often the most common culprits. Careful attention should be paid to the administration of nephrotoxic agents and intravenous contrast agents, correction of fluid depletion and over-diuresis, and exclusion of intrinsic renal problems which are common place in patients with alcoholic liver disease, viral hepatitis, and those with diabetes.

Assessing renal function in this cohort is extremely challenging and serum creatinine may not be an accurate representation in patients with poor muscle mass and hyperbilirubinemia. Consequently, a 24 hour creatinine clearance is often more accurate than an estimated glomerular filtration rate. A spot urinary sodium measurement can be invaluable in differentiating acute tubular necrosis (urinary sodium > 40 mmol/l) from pre-renal causes and hepatorenal syndrome (urinary sodium < 10 mmol/l). Renal failure may be the only manifestation of sepsis and patients with spontaneous bacterial peritonitis are particularly vulnerable to developing renal dysfunction. The clinical problem is therefore of distinguishing pre-renal failure due to sepsis, hypovolemia, or hepatorenal syndrome, from acute tubular necrosis and it is interesting to note the significant similarities between pre-renal failure as seen commonly in the critical care setting and hepatorenal syndrome. Regardless of the eventual diagnosis, the initial approach is the same in all patients who will be volume deplete. Fluid resuscitation with 1.5 l of colloid or crystalloid is

thus the first management step in this cohort. Other causes of renal failure such as virally driven glomerulonephritis, intersitial nephritis, and IgA nephropathy should be considered.

Treatment of hepatorenal syndrome with vasopressin or vasopressin analogs is based on the principle that hepatorenal syndrome results from a reduction in effective arterial blood volume due to arterial vasodilatation and, therefore, that vasoconstrictor drugs may be of benefit. Terlipressin has been evaluated in type 1 hepatorenal syndrome in several studies and has been effective in reversing hepatorenal syndrome in the majority of patients and associated with increased survival, although skeptics have often felt that this may be a reflection on the fact that those given terlipressin (with and without albumin) were more aggressively fluid resuscitated than controls (reviewed in [47]). Data to support the co-administration of albumin and terlipressin have recently been proposed as not only does albumin serve as a volume expander but it has other roles such as an anti-oxidant [48].

Renal replacement therapy is often instituted too late in the course of illness and data is emerging to suggest that it may also dampen down the manifestation of SIRS and reduce arterial ammonia. Studies in the field of renal replacement therapy do not demonstrate any clear benefit of continuous therapies as compared to intermittent ones. Intuitively however, continuous therapy is more likely to be suitable in hemodynamically unstable patients with cirrhosis with metabolic disarray and the risk of cerebral dysfunction [49].

Respiratory

The causes of hypoxia in patients with acute-on-chronic liver failure are diverse and include chest sepsis, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), splinting of the diaphragms from tense ascites, hepatic hydrothorax, hepatopulmonary syndrome, and pulmonary edema. Some patients may also have intrinsic lung disease, either as part of their liver disease, e.g., alpha-1 antitrypsin deficiency and cystic fibrosis, associated with fibrosing lung disease, or unrelated to their liver disease. Furthermore, the airway is at risk in patients with acute variceal bleeding and severe hepatic encephalopathy. Airway protection is paramount in the latter two populations who have been shown to have good outcomes when managed early and aggressively in a critical care rather than ward environment. It is also important to bear in mind that these patients are immunosuppressed and are at risk of opportunistic fungal infections and cytomegalovirus re-activation.

Bubble echocardiography is a useful tool in the diagnosis of hepatopulmonary syndrome and shunting. This is caused by arteriovenous shunting in the lung leading to a ventilation-perfusion mismatch and hypoxia which improves in the supine position and worsens on sitting/standing.

XV Conclusion

Although consensus has yet to be reached on the precise definition of acute-on-chronic liver failure, it can be viewed simply as the development of one or more organ(s) dysfunction in a patient with cirrhosis. The more organs affected, the bleaker the long-term prognosis in the absence of liver transplantation. It is important not to disregard the impact of hepatic dysfunction on the adrenals, immune system, and gut. The key management principle in the critically ill patient with cirrhosis is

to administer early aggressive goal-directed therapies and to remember that admission to a critical care environment is not futile, particularly for those with single organ failure, acute variceal bleeding, and severe hepatic encephalopathy. Management should focus on treating precipitating factors such as infection, metabolic disarray, and hypovolemia. It can be extremely challenging to manage patients with organ dysfunction and hepatic encephalopathy in a ward environment and these patients frequently require, and indeed benefit from, augmented levels of care in high-dependency and intensive care facilities.

References

1. Sen S, Davies NA, Mookerjee RP, et al (2004) Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transpl 10: 1109 – 1119
2. Gildea TR, Cook WC, Nelson DR, et al (2004) Predictors of long-term mortality in patients with cirrhosis of the liver admitted to a medical ICU. Chest 126: 1598 – 1603
3. Cholongitas E, Senzolo M, Patch D, et al (2006) Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. Aliment Pharmacol Ther 23: 883 – 893
4. Zimmerman JE, Wagner DP, Seneff MG, Becker RB, Sun X, Knaus WA (1996) Intensive care unit admissions with cirrhosis: risk-stratifying patient groups and predicting individual survival. Hepatology 23: 1393 – 1401
5. Shawcross D, Austin M, Abeles R, et al (2008) Defining the impact of organ dysfunction in cirrhosis: survival at a cost? Gut 57 (Suppl 1):A12-A13 (abst)
6. Levy M, Fink M, Marshall J, et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 29: 530 – 538
7. Rivers E, Nguyen B, Havastad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368 – 1377
8. Knaus W, Draper E, Wagner D, Zimmerman J (1985) Prognosis in acute organ-system failure. Ann Surg 202: 685 – 693
9. Vincent JL, Moreno R, Takala J, et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22: 707 – 710
10. Austin M, Shawcross D (2008) Outcome of patients with cirrhosis admitted to intensive care. Curr Opin Crit Care 14: 202 – 207
11. Pugh R, Murray-Lyon I, Dawson J, Pietroni M, Williams R (1973) Transection of the oesophagus for bleeding oesphageal varices. Br J Surg 60: 646 – 649
12. Kamath K, Weisner R, Malinchoc M, et al (2001) A model to predict survival in patients with end-stage liver disease. Hepatology 33: 464 – 470
13. Jenq C, Tsai M, Tain Y, et al (2007) RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. Intensive Care Med 33: 1921 – 1930
14. Wasmuth H, Kunz D, Yagmur E, et al (2005) Patients with acute on chronic liver failure display 'sepsis-like' immune paralysis. J Hepatol 42: 195 – 201
15. Wong F, Bernardi M, Balk R, et al (2005) Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 54: 718 – 725
16. Antoniades CG, Berry PA, Davies ET, et al (2006) Reduced monocyte HLA-DR expression: a novel biomarker of disease severity and outcome in acetaminophen-induced acute liver failure. Hepatology 44: 34 – 43
17. Jalan R, Newby DE, Damink SW, Redhead DN, Hayes PC, Lee A (2001) Acute changes in cerebral blood flow and metabolism during portasystemic shunting. Liver Transpl 7: 274 – 278
18. Van der Linden P, Le Moine O, Ghysels M, Ortinez M, Deviere J (1996) Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. Hepatology 23: 982 – 987
19. Harry R, Auzinger G, Wendon J (2002) The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology 36: 395 – 402
20. Marik P, Gayowski T, Starzl T (2005) The hepatoadrenal syndrome: a common yet unrecognised clinical condition. Crit Care Med 33: 1254 – 1259

21. Fernandez J, Escorsell A, Zabalza M, et al (2006) Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. Hepatology 44: 1288 – 1295
22. Ferenci P, Lockwood A, Mullen K, et al (2002) Hepatic Encephalopathy – Definition, nomenclature, diagnosis and quantification: Final report of the Working Party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatology 35: 716 – 721
23. Cordoba J, Alonso J, Rovira A, et al (2001) The development of low-grade cerebral oedema in cirrhosis is supported by the evolution of 1H-magnetic resonance abnormalities after liver transplantation. J Hepatol 35: 598 – 604
24. Als-Nielsen B, Gluud L, Gluud C (2004) Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 328: 1046 – 1050
25. Cordoba J, Lopez-Hellin J, Planas M, et al (2004) Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 41: 38 – 43
26. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R (2000) The systemic inflammatory response syndrome in acute liver failure. Hepatology 32: 734 – 739
27. Shawcross D, Davies N, Williams R, Jalan R (2004) Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol 40: 247 – 254
28. Liu Q, Duan ZP, Ha dK, Bengmark S, Kurtovic J, Riordan SM (2004) Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 39: 1441 – 1449
29. Hassanein T, Tofteng F, Brown R, et al (2007) Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology 46: 1853 – 1862
30. Bernal W, Auzinger G, Sizer E, Wendon J (2008) Intensive care management for acute liver failure. Semin Liver Dis 28: 188 – 200
31. Chau T, Chan Y, Patch D, Tokanuga S, Greenslade L, Burroughs A (1998) Thrombelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding. Gut 43: 267 – 271
32. Papatheodoridis G, Patch D, Webster G, Brooker J, Barnes E, Burroughs A (1999) Infection and hemostasis in decompensated cirrhosis: a prospective study using thrombelastography. Hepatology 29: 1085 – 1090
33. Fernandez-Seara J, Prieto J, Quiroga J, et al (1989) Systemic and regional haemodynamics in patients with liver cirrhosis and ascites with and without functional renal failure. Gastroenterology 97: 1304 – 1312
34. Moller S, Henriksen J (2008) Cardiovascular complications of cirrhosis. Gut 57: 268 – 278
35. Russell J, Walley K, Singer J, et al (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358: 877 – 887
36. Annane D, Sebille V, Charpentier C, et al (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288: 862 – 871
37. Malbrain M, Chiumello D, Pelosi P, et al (2004) Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. Intensive Care Med 30: 822 – 829
38. Rajkovic IA, Williams R (1986) Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. Hepatology 6: 252 – 262
39. Trevisani F, Castelli E, Foschi FG, et al (2002) Impaired tuftsin activity in cirrhosis: relationship with splenic function and clinical outcome. Gut 50: 707 – 712
40. Mookerjee R, Stadlbauer V, Lidder S, et al (2007) Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts outcome. Hepatology 46: 831 – 840
41. Shawcross D, Wright G, Stadlbauer V, et al (2008) Ammonia impairs neutrophil phagocytic function in liver disease. Hepatology 48: 1202 – 1212
42. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F (2000) Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis 32: 605 – 610
43. Olde Damink S, Jalan R, Deutz N, et al (2003) The kidney plays a major role in the hyperammonemia seen after a simulated or actual upper gastrointestinal bleeding in patients with cirrhosis. Hepatology 37: 1277 – 1285
44. Walker S, Stiehl A, Raedsch R, Kommerell B (1986) Terlipressin in bleeding oesphageal varices: a placebo-controlled, double blind study. Hepatology 6: 112 – 115

45. Monescillo A, Martinez-Lagares F, Ruiz-del-Arbol L, et al (2004) Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 40: 793 – 801
46. Laine L, Planas R, Nevens F, Banares R, Patch D, Bosch J (2006) Treatment of the acute bleeding episode. In: De Franchis R (ed) Portal Hypertension IV: Proceedings of the Fourth Baveno International Consensus Workshop. Blackwell Publishing, Boston, pp217 – 242
47. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V (2007) Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 56: 1310 – 1318
48. Ortega R, Gines P, Uriz J, et al (2002) Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, non randomised study. Hepatology 36: 941 – 948
49. VA/NIH Acute Renal Failure Trial Network (2008) Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359: 7 – 20