Renal failure in chronic liver disease and the hepatorenal syndrome

Hepatorenal syndrome is a distinctive complication of cirrhosis. Advances in understanding its pathogenesis have lead to new treatments with improved outcomes. This article focuses on evidence-based management of renal failure in cirrhosis including hepatorenal syndrome, in the context of pathophysiological changes that occur.

Most patients with established cirrhosis develop one or more features of decompensated liver disease, which include variceal haemorrhage, ascites, hepatic encephalopathy, the hepatopulmonary syndrome and renal impairment often in association with, or precipitated by, sepsis. Malnutrition and hepatocellular carcinoma are other important complications of cirrhosis. The onset of any of these complications signals substantial change in the likelihood of death from liver disease and alerts clinicians to consider alternative strategies, including liver transplantation. In particular the onset of renal impairment in cirrhosis denotes a substantial increase in mortality (du Cheyron et al, 2005). The Child–Turcotte–Pugh model (*Table 1*), used for decades to predict liver-related mortality, has been supplanted by more accurate UK model for end-stage liver disease (UKELD) or model for end-stage liver disease (MELD) scores, which include serum creatinine levels. These are easy to access and are used widely to identify patients for liver transplant assessment and listing, as well as prioritizing patients on the liver transplant waiting list, reflecting the importance of renal function in advanced chronic liver failure (*Table 2*). The online calculator for the UKELD score can be accessed via the following link: www.uktransplant.org.uk/ukt/about_transplants/organ_allocation/liver/liver.jsp.

Renal failure in chronic liver disease can be divided into well-known, distinct categories, i.e. acute and chronic renal failure (kidney injury). Acute renal failure occurs in approximately 20% of patients with cirrhosis who are hospitalized for hepatic decompensation (Hampel et al, 2001; Wu et al, 2006). Chronic renal failure is likely to be a manifestation of unrelated renal pathology or, less often, systemic disease affecting both liver and kidney, such as chronic viral hepatitis, diabetes mellitus (with non-alcohol related fatty liver disease) or polycystic liver disease (associated with polycystic kidney disease).

An overview of the underlying pathophysiological mechanisms and management of acute renal failure complicating cirrhosis are the main focus of this article.

Definitions

The term acute renal failure was replaced by acute kidney injury based on the consensus report of the Acute Kidney Injury Network in 2007, and encompasses all causes of acute renal failure. The classification is based on disease severity (Mehta et al, 2007). Acute kidney injury is defined as sudden deterioration in kidney function

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Table 1. Child–Turcotte–Pugh scoring system

Child–Turcotte–Pugh score	1 point	2 points	3 points
Total bilirubin (μmol/litre)	<34	34–50	>50
Serum albumin (g/litre)	>35	28–35	<28
International normalized ratio	<1.7	1.7–2.2	>2.2
Ascites	None	Mild	Severe
Encephalopathy	None	Grade I–II	Grade III–IV

Table 2. Implications of Child–Turcotte–Pugh, model for end-stage liver disease and UK model for end-stage liver disease scores

Model	Parameters/mathematical formula	Comments
Child–Turcotte–Pugh	Class A = 5–6 points, class B = 7–9 points, class C = 10–15 points (*Table 1*)	1-year survival: class A = 100%; class B = 81%; class C = 45%
Model for end-stage liver disease score	3.78 (ln serum bilirubin (mg/dl)) +11.2 (ln INR) + 9.57 (ln serum creatinine (mg/dl)) + 6.43	3-month mortality: <9 = 1.9%; 10–19 = 6%; 20–29 = 19.6%; 30–39 = 52.6%; >40 = 71.3%
UK model for end-stage liver disease score	5 x (1.5 x ln (INR) + 0.3 x ln (creatinine) + 0.6 x ln (bilirubin) – 13 x ln (Na) + 70)	1-year mortality: >49 = >9%; >60 = >50%

INR = international normalized ratio; ln = natural log.

(within 48 hours) measured by an absolute increase in serum creatinine level of ≥26.4 μmol/litre, percentage increase in serum creatinine level of ≥1.5-fold from baseline or a urine output less than 0.5 ml/kg per hour for over 6 hours. The definition divides the severity of renal dysfunction into three types, based on changes in serum creatinine level or urine output after excluding urinary tract obstruction (*Table 3*).

Table 3. Acute Kidney Injury Network classification of acute kidney injury

	Increase in serum creatinine (μmol/litre)	Urine output (ml/kg/h)
Stage 1 (defines acute kidney injury)	>26.4 μmol/litre or >150–200% change from baseline	<0.5 for >6 hours
Stage 2	>200–300% change from baseline	<0.5 for >12 hours
Stage 3	>300% change from baseline (or serum creatinine ≥354 μmol/litre) with an acute increase of ≥44 μmol/litre	

From Mehta et al (2007)

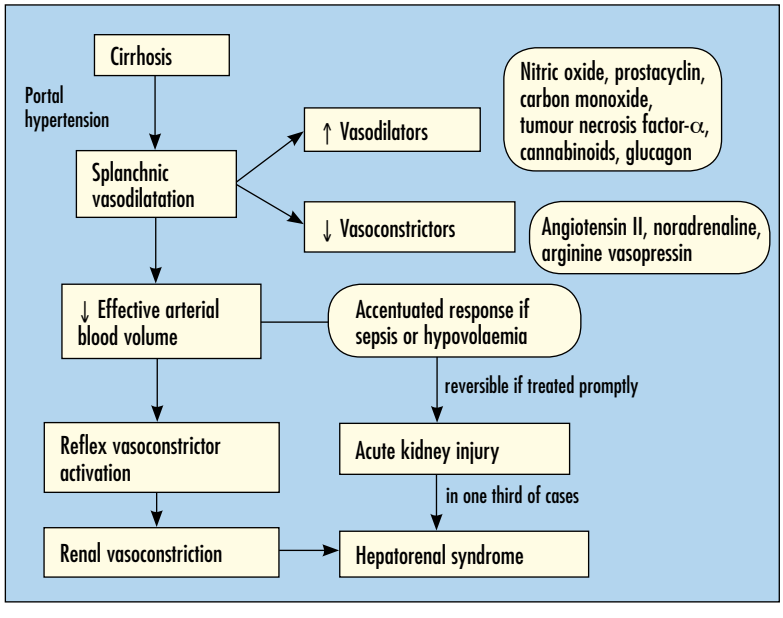
Table 4. Causes of acute kidney injury in chronic liver disease

Pre-renal causes	Volume-responsive condition: infection, hypovolaemia, vasodilators, diuretics
	Hepatorenal syndrome (type 1)
Acute tubular necrosis	
Drug induced (non-steroidal anti-inflammatory drugs, aminoglycosides and angiotensin-converting enzyme inhibitors)	

Table 5. Causes of chronic kidney disease in chronic liver disease

Hepatitis C virus-related membranoproliferative glomerulonephritis
Hepatitis B virus-related membranous nephropathy
Diabetic nephropathy (as part of non-alcoholic steatohepatitis or metabolic syndrome)
Hepatorenal syndrome (type 2)
Alcohol-related immunoglobulin A nephropathy

Figure 1. Pathophysiology of hepatorenal syndrome and acute kidney injury in cirrhosis.



Serum creatinine is measured readily and universally to assess renal function, but age, gender, ethnicity, nutritional state and liver disease all influence serum creatinine levels and must be considered when estimating renal function (Tomlanovich et al, 1986; Takabatake et al, 1988). Patients with chronic liver disease and renal impairment are more likely to be older males with poor nutrition and a lower baseline serum creatinine level than the general population (Slack et al, 2010).

Aetiology

The most likely cause of acute kidney injury in any patient with cirrhosis is hypovolaemia, for which there are many explanations but pre-renal failure is so common in this context that fluid resuscitation is usually a good starting point. A systematic review (Garcia-Tsao et al, 2008) showed that acute kidney injury occurred in two thirds of hospitalized cirrhotic patients; a further third had intrinsic renal disease while a tiny proportion (<1%) had post-renal disease. Two thirds of patients with pre-renal aetiology had reversible, volume-responsive conditions such as sepsis or hypovolaemia while a third had the hepatorenal syndrome (type 1 or 2). Similar findings were observed in 463 patients with cirrhosis and acute kidney injury (Martín-Llahí et al, 2011); the cause in four fifths was pre-renal (again related to sepsis or hypovolaemia) and the remainder were split between hepatorenal syndrome and intrinsic renal disease. *Tables 4* and *5* list causes of acute kidney injury and chronic kidney disease in cirrhosis.

Circulatory changes in cirrhosis

Characteristic circulatory disturbances in cirrhosis worsen with progressive liver failure and are manifest as a hyperdynamic circulation, with reduced systemic blood pressure, a bounding pulse and tachycardia. Portal hypertension is believed to be the primary event leading to splanchnic circulation vasodilatation (Abraldes et al, 2006) and subsequently systemic circulation vasodilatation. The same changes occur with portal hypertension without cirrhosis. It is probable that the effects of portal hypertension are mediated by a complex of proven vasodilator molecules, which exert direct effects on the splanchnic bed (Iwakiri and Groszmann, 2006). The best studied of these molecules include nitric oxide, carbon monoxide and endogenous cannabinoids (Ros et al, 2002; Iwakiri and Groszmann, 2006).

Systemic and splanchnic vasodilatation reduces effective arterial blood volume so that patients with cirrhosis develop hypovolaemia (*Figure 1*). The homeostatic response to hypovolaemia leads to activation of the neurohumoral systems, particularly the renin–aldosterone axis, sympathetic nervous system and non-osmotic secretion of antidiuretic hormone (Schrier, 1988), lead-

ing to sodium and water retention. Plasma expansion restores blood volume towards normal. Patients with early cirrhosis without ascites or oedema have subclinical reductions in blood volume and retention of sodium and water. Simultaneously, increased cardiac output compensates for reduced peripheral vascular resistance (Guyton, 1980), with increased venous return to the heart, leading to the characteristic hyperdynamic circulation (Genecin et al, 1990). Patients with cirrhosis are especially vulnerable to factors that reduce the circulating volume further.

Systemic vasodilatation alone is rarely sufficient to compromise renal function, as portal hypertension evolves at a rate that allows the compensatory reflex mechanisms in the splanchnic bed to maintain effective blood volume and organ perfusion (Ginès et al, 2007). However, with a hyperdynamic circulation, any further compromise in blood volume caused by acute and rapid fluid loss leads to further decreases in effective arterial blood volume, renal vasoconstriction and pre-renal compromise. The most common causes are infection, haemorrhage and dehydration following inappropriate diuretic use and unrecognized hypovolaemia.

With worsening portal hypertension there is further reduction in systemic and splanchnic vascular resistance leading to reduction in effective arterial circulation and consequently a decrease in cardiac pre-load. Intrinsic cardiac dysfunction may also develop with advanced liver disease manifest as attenuated systolic and diastolic function and a negative chronotropic effect, termed cirrhotic cardiomyopathy (beyond the scope of this article) (Mandell et al, 2008). Further activation of neurohumoral reflexes to maintain adequate arterial volume causes further salt and water retention and eventually ascites and oedema develop. Uncorrected, these changes lead to intense renal vasoconstriction (via the renin–angiotensin system and sympathetic activation) with further reductions in glomerular filtration and renal perfusion pressure, leading eventually to acute kidney injury. These circulatory changes, in conjunction with acute kidney injury, constitute the hepatorenal syndrome (Arroyo et al, 2008).

Investigations in acute kidney injury

Helpful investigations include urine dipstick analysis for haematuria or proteinuria, renal ultrasound, vasculitis screen, urinary sodium and fractional excretion of sodium, and assessment of sepsis and hypovolaemia. The fractional excretion of sodium helps distinguish between hepatorenal syndrome and acute tubular necrosis, since renal tubular function is preserved in patients with acute kidney injury caused by volume responsive conditions and hepatorenal syndrome, but not in acute tubular necrosis. Typically, patients with hypovolaemia and hepatorenal syndrome have low urinary sodium (<20 mEq/litre) and fractional excretion of sodium (<1%), while patients with acute tubular necrosis have high urinary sodium (>40 mEq/litre) and fractional excretion of sodium (≥2%). Diuretic therapy increases urinary sodium and fractional excretion of sodium, so interpret results with caution in diuretic-treated patients.

Treatment of acute kidney injury

Circulatory changes are critical in the development of acute kidney injury. A simple strategy to halt or ameliorate plasma volume expansion, at least in the early stages, is dietary salt (Na) restriction to 60–80 mmol/day, which prevents further accumulation of ascites and oedema and is recommended. Consider gastrointestinal haemorrhage or hypovolaemia in patients with hypotension. Review drug charts for agents that cause hypotension or are nephrotoxic. Resuscitate with intravenous fluid (human albumin solution or gelofusine), depending upon clinical status and serum albumin level. If serum albumin level is <25 g/dl, 20% human albumin solution (100 ml boluses) should be given (20–40 g/day) or 4.5% human albumin solution (500 ml every 4–6 hours) with hypovolaemia. Close monitoring of haemodynamic status and fluid balance is mandatory to avoid fluid overload and is aided by catheterization to maintain central venous pressure between 10 and 12 cmH_2O. Avoid use of normal saline which worsens ascites and oedema in the presence of sodium retention.

Infection increases morbidity and mortality. Early identification of infection, prompt treatment with broad spectrum antibiotics and correction of hypovolaemia are crucial. Sepsis screens should be performed whenever infection is suspected.

About 20% of those with decompensated chronic liver disease develop spontaneous bacterial peritonitis (Sheer and Runyon, 2005), precipitating acute kidney injury in a third; diagnostic ascitic tap confirms spontaneous bacterial peritonitis (neutrophil count > 250 cells/mm^3). If confirmed start antibiotics after culture of blood and ascites have been taken. Albumin infusion reduces the risk of hepatorenal syndrome and improves survival (Sort et al, 1999). After successful treatment, convert patients to long-term antibiotic prophylaxis to reduce the risk of developing hepatorenal syndrome (Fernandez et al, 2007).

If patients fail to respond to these interventions and renal function worsens, consider renal support and referral to tertiary liver units.

Hepatorenal syndrome

Hepatorenal syndrome, first described in 1932 (Helvig and Schutz, 1932), is reversible functional renal failure with a high mortality that occurs in cirrhosis, usually with ascites and characterized by circulatory and renal dysfunction in the absence of pre-existing intrinsic or parenchymal renal disease.

Hepatorenal syndrome was the third most common cause of admission to intensive care among 420 cir-

rhotic patients, after upper gastrointestinal haemorrhage and encephalopathy (Gildea et al, 2004). Nearly one third of patients with acute kidney injury and cirrhosis have hepatorenal syndrome. Cirrhosis is not a prerequisite for hepatorenal syndrome; half with acute liver failure and one third with severe acute alcoholic hepatitis develop hepatorenal syndrome (Moore, 1999; Verma et al, 2006).

Modified diagnostic criteria for hepatorenal syndrome defined by the International Ascites club are shown in *Table 6*. Type 1 hepatorenal syndrome is characterized by rapid progression of renal failure in the context of acute circulatory changes and characterized by arterial hypotension, reflex activation of endogenous vasoactive systems and impaired cardiac function, and has a very high mortality. Type 2 hepatorenal syndrome pursues a slower course with moderate chronic renal dysfunction; arterial vasodilatation is associated with preserved cardiac function. *Table 7* lists key differences between type 1 and type 2 hepatorenal syndrome.

Table 6. Diagnostic criteria for hepatorenal syndrome

Cirrhosis with ascites
Serum creatinine >133 μmol/litre
No improvement in serum creatinine (decrease to a level of <133 μmol/litre) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg body weight per day to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as assessed by proteinuria >500 mg/day, microscopic haematuria (>50 red blood cells/high power field) and/or abnormal renal ultrasonography

From Salerno et al (2007)

Table 7. Differences between type 1 and type 2 hepatorenal syndrome

	Type 1	Type 2
Definition	Abrupt rise in serum creatinine within 2 weeks to >226 μmol/litre	Moderate renal failure with creatinine = 133–226 μmol/litre
Clinical course	Rapidly progressive (<2 weeks)	Steady or slowly progressive
Clinical pattern	Acute kidney injury	Refractory ascites
Onset	Often precipitated by spontaneous bacterial peritonitis or infection but may appear spontaneously	Usually appears spontaneously but can follow precipitating event
Cardiac function	Often impaired	Usually well preserved
Survival*	Median survival = 1 month	Median survival = 6.7 months
Progression	–	Can develop type 1 hepatorenal syndrome if acute circulatory dysfunction present

* from Alessandria et al (2005)

Pathophysiology

The principal haemodynamic change in hepatorenal syndrome is arterial hypotension caused by reduced systemic vascular resistance and reduced effective cardiac output. The pathophysiological hallmark of hepatorenal syndrome is intense renal vasoconstriction mediated by reflex vasoconstriction (renin–angiotensin, sympathetic reflex systems and antidiuretic hormone) which is activated in response to splanchnic vasodilatation triggered by portal hypertension, leading to reduced renal perfusion and glomerular filtration rate but conserved tubular function. Renal histology is normal and kidneys resume normal function after liver transplantation.

Increased antidiuretic hormone secretion leads to sodium and water retention in the distal tubules resulting in dilutional hyponatraemia akin to syndrome of inappropriate antidiuretic hormone secretion and worsening of ascites. Patients most at risk of hepatorenal syndrome are those with avid sodium retention in the presence of ascites and dilutional hyponatraemia (Ginès et al, 1993).

Hepatorenal syndrome can occur spontaneously in the setting of ascites or can be precipitated by secondary events such as infection, haemorrhage or large volume paracentesis without albumin cover (Cardenas et al, 2001). Bacterial infection, particularly spontaneous bacterial peritonitis, is the most important risk factor for hepatorenal syndrome: 81% with cirrhosis and spontaneous bacterial peritonitis who did not respond to antibiotic treatment developed progressive renal failure compared to 7% of antibiotic-responsive patients (Follo et al, 1994). In patients with sepsis unrelated to spontaneous bacterial peritonitis, 55% of non-responders developed progressive renal failure compared to 1% of antibiotic-responsive patients (Terra et al, 2005). A small proportion with spontaneous bacterial peritonitis develops progressive renal failure despite effective antibiotic treatment, but in most renal failure resolves after effective antibiotic therapy. Risk factors for renal failure after bacterial infection are severity of infection, failure to respond to treatment and MELD score (Terra et al, 2005; Fasolato et al, 2007).

Changes in circulatory function and renal function in patients who develop renal failure as a result of spontaneous bacterial peritonitis or sepsis are identical to those who develop hepatorenal syndrome spontaneously, suggesting similar underlying pathophysiolological mechanisms (Salerno et al, 2007).

Treatment of hepatorenal syndrome

The only definitive treatment for hepatorenal syndrome is liver transplantation, although hepatorenal syndrome at transplantation affects the postoperative transplant outcome adversely. Current treatment modalities often serve as a bridge to transplantation. Effective treatment in hepatorenal syndrome should increase both effective arte-

rial volume (by increasing the central plasma volume) and systemic vascular resistance to achieve and maintain adequate renal perfusion. Recent studies show that vasoconstrictor drugs, particularly vasopressin analogues, may be effective.

Vasoconstrictors

A meta-analysis (Gluud et al, 2010) of 10 randomized trials compared different vasoconstrictors in hepatorenal syndrome (type 1 or 2) with all-cause mortality as primary outcome. Secondary outcomes included: reversal of hepatorenal syndrome (serum creatinine <133 μmol/litre), improved renal function (>50% improvement in serum creatinine) and adverse events. All but one trial compared terlipressin (with or without albumin) to placebo, albumin or noradrenalin (with albumin). One trial compared octreotide (with albumin) *vs* albumin alone. Key findings were that vasoconstrictors (with or without albumin) reduced mortality at 15 days but not beyond 30 days, increased the proportion with reversal of hepatorenal syndrome and improved renal function. Terlipressin was found superior to other vasoconstrictors with its efficacy enhanced by albumin, but adverse cardiovascular events included arrhythmia, myocardial infarction, intestinal or peripheral ischaemia and systemic hypertension (Gluud et al, 2010).

Terlipressin (a long-acting vasopressin analogue administered as boluses) mediates vasoconstriction by activating vasopressin 1 (V1) receptors expressed preferentially on vascular splanchnic smooth muscle. Terlipressin causes mesenteric vasoconstriction, reducing portal blood flow and augments effective systemic arterial circulation. A study in cirrhosis without ascites revealed that terlipressin increased mean arterial pressure and systemic vascular resistance, but decreased renal arterial resistance, plasma rennin activity and portal blood flow. It appears that terlipressin does not cause hepatic arterial vasoconstriction and so may maintain hepatic oxygenation (Narahara et al, 2009).

Role of albumin

Albumin improves circulatory function by increasing central plasma volume and consequently pre-load to the heart. It also increases peripheral vascular resistance and prevents deterioration of renal function in patients with spontaneous bacterial peritonitis (Fernandez et al, 2004). Terlipressin and albumin have different actions, which may explain why they are more effective in combination.

Treatment dose and duration

At first, terlipressin (0.5–1 mg) is given 4–6-hourly, to be continued until reversal of hepatorenal syndrome (serum creatinine <133 μmol/litre), within 10–14 days if at all. If the creatinine level does not improve within 48–72 hours the dose can be increased up to 2 mg every 6 hours but ischaemia is very common and hazardous at these doses. Patients should be adequately fluid resuscitated before commencing terlipressin, as it has the potential to worsen the situation in absence of adequate plasma volume expansion. Central venous pressures should be monitored in all patients to assess fluid balance.

Albumin

The recommended dose for albumin infusion is 1 g/kg (maximum 100 g/day) on day 1 followed by 20–40 g/day. It is essential that central venous pressure is maintained between 10 and 12 cmH_2O in hepatorenal syndrome.

Reversal of hepatorenal syndrome is achieved in two thirds of patients treated with terlipressin and albumin and more have some improvement in renal function, but it recurs in nearly 20%; re-treatment is often effective (Salerno et al, 2007).

Boyer et al (2011) concluded that baseline serum creatinine level is the single best predictor of response to hepatorenal syndrome treatment. Patients with early onset and moderate renal failure (serum creatinine <266 μmol/litre) are most likely to benefit from treatment with terlipressin (with albumin). Interestingly, terlipressin was most effective with serum creatinine between 266–443 μmol/litre; more advanced renal failure was unlikely to respond to vasoconstrictor therapy. Reversal of hepatorenal syndrome was associated with a sustained increase in mean arterial pressure rather than an isolated rise (Boyer et al, 2011), providing further evidence that terlipressin improves renal perfusion. Treatment with terlipressin should be discontinued in patients who do not respond within 14 days.

Transjugular intrahepatic porto-systemic shunts

Transjugular intrahepatic portosystemic shunting improves renal function in patients with both type 1 and type 2 hepatorenal syndrome. It seems plausible that transjugular intrahepatic portosystemic shunting may have a role in bridging to transplantation, but there are insufficient data to recommend its use as a routine treatment.

Liver transplantation

Liver transplantation is the only definitive treatment for both type 1 and type 2 hepatorenal syndrome with renal recovery after transplantation and in some cases perioperatively. However, patients with hepatorenal syndrome have more complications in the postoperative period and often require temporary dialysis. Mortality is higher in this group; 3-year survival after transplant for hepatorenal syndrome is 60% as compared to 70–80% in patients without hepatorenal syndrome.

Specific treatment for type 2 hepatorenal syndrome

Refractory ascites is the commonest finding, when repeated paracentesis with intravenous albumin (8 g of albumin for each litre of ascites removed) is the preferred

treatment. *Table 8* outlines tips for safe management of ascites. In patients requiring frequent large-volume paracentesis, transjugular intrahepatic portosystemic shunting is a suitable alternative but associated with a high risk of hepatic encephalopathy. Few patients with type 2 hepatorenal syndrome have been treated with terlipressin and albumin. In most, normalization of serum creatinine was observed but, in contrast to type 1 hepatorenal syndrome, renal failure invariably recurred after treatment withdrawal (Moreau and Lebrec, 2006).

Conclusions

Acute kidney injury and hepatorenal syndrome occur as a result of changes in circulatory function in the presence of chronic liver disease. Pathophysiological hallmarks include splanchnic vasodilatation (triggered by portal hypertension) and activation of reflex vasoactive pathways. It is associated with increased morbidity and mortality and warrants prompt investigation and treatment of the underlying cause. Treatment is often effective when initiated in the early stages. In advanced stages, prognosis is often guarded and therapy should be tailored as per individual needs. Patients should be assessed early for consideration of liver transplantation and case discussed with a tertiary liver unit. BJHM

Table 8. Safe management of ascites

Non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors should be stopped
Aminoglycoside use should be avoided
Contrast medium should be used with caution with renal impairment
Paracentesis should always be done with albumin cover (8 g for each litre of ascites removed)
Patients on diuretics should have regular clinical and biochemical monitoring
Maximum recommended weight loss during diuretic therapy should be 0.5 kg/day in patients without oedema and 1 kg/day in patients with oedema

From European Association for the Study of the Liver (2010)

KEY POINTS

- Acute kidney injury and hepatorenal syndrome is associated with high morbidity and mortality but is potentially treatable.
- Sepsis should be excluded in all patients and treated promptly if present.
- Terlipressin should not be given first without plasma volume expansion.
- Central venous pressure monitoring is essential in patients with worsening renal failure.
- 20% human albumin solution must be given to patients with spontaneous bacterial peritonitis and hepatorenal syndrome unless contraindicated.
- Management of acute kidney injury and hepatorenal syndrome should be discussed early with a specialist liver unit.
- Liver transplantation should be considered early in patients with hepatorenal syndrome.

Conflict of interest: none.

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