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REVIEW

Acute renal dysfunction in liver diseases

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Abstract

Renal dysfunction is common in liver diseases, either as part of multiorgan involvement in acute illness or secondary to advanced liver disease. The presence of renal impairment in both groups is a poor prognostic indicator. Renal failure is often multifactorial and can present as pre-renal or intrinsic renal dysfunction. Obstructive or post renal dysfunction only rarely complicates liver disease. Hepatorenal syndrome (HRS) is a unique form of renal failure associated with advanced liver disease or cirrhosis, and is characterized by functional renal impairment without significant changes in renal histology. Irrespective of the type of renal failure, renal hypoperfusion is the central pathogenetic mechanism, due either to reduced perfusion pressure or increased renal vascular resistance. Volume expansion, avoidance of precipitating factors and treatment of underlying liver disease constitute the mainstay of therapy to prevent and reverse renal impairment. Splanchnic vasoconstrictor agents, such as terlipressin, along with volume expansion, and early placement of transjugular intrahepatic portosystemic shunt (TIPS) may be effective in improving renal function in HRS. Continuous renal replacement therapy (CRRT) and molecular absorbent recirculating system (MARS) in selected patients may be life saving while awaiting liver transplantation.

Key words: Hepatorenal syndrome; Transjugular intrahepatic portosystemic shunt; Continuous renal replacement therapy; Molecular absorbent recirculating system; Acute liver failure; Systemic vascular resistance; Renal blood flow

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INTRODUCTION

Renal and liver dysfunction often present together, either as part of multiorgan failure in a critically ill patient, or as a result of failure of each organ independently. Three major clinical scenarios can be identified in which liver and renal dysfunction coexist; diseases simultaneously involving the liver and the kidney, or a primary hepatic disorder with secondary renal dysfunction, or vice versa[1]. Concomitant renal and liver dysfunction may share common pathogenetic mechanisms. Renal dysfunction in this setting usually develops gradually, with the exception of certain infections such as leptospirosis, some viral hemorrhagic fevers and toxin-mediated injuries such as acetaminophen poisoning, which cause acute insufficiency of both organs[2]. Renal failure secondary to liver dysfunction is generally functional in nature and occurs in the absence of significant alterations in renal histology (pre-renal). However, intrinsic renal abnormalities can also complicate acute or chronic liver disease (intrinsic renal failure)[3]. Obstructive uropathy that leads to postrenal acute renal failure only rarely develops in chronic liver disease (papillary necrosis in alcoholic liver disease, bleeding in the urinary tract due to severe coagulopathy)[4]. Hepatorenal syndrome (HRS) is a unique form of functional renal failure (pre-renal) that often complicates advanced liver disease, hepatic failure or portal hypertension[5].

EPIDEMIOLOGY

The incidence of renal failure in acute liver failure (ALF) varies from 40% to 85%, depending on the etiology; paracetamol poisoning leads to renal failure in up to 75% of patients[6]. Renal failure following paracetamol overdose may also occur in the absence of ALF, and has a good prognosis[7]. In non-paracetamol cases the incidence of renal failure is usually accompanied by worsening encephalopathy and is associated with a poor outcome[5,6].

Acute renal failure (ARF) in patients with cirrhosis, particularly with advanced liver disease, seems to be common; however, the exact incidence is unknown and is probably underestimated[3]. This may be explained by the fact that patients with cirrhosis tend to have falsely low serum creatinine levels due to decreased hepatic creatinine synthesis and decreased skeletal muscle mass[8]. ARF in patients with cirrhosis frequently accompanies complications such as bacterial peritonitis or other

sepsis, hypovolemia from gastrointestinal bleeding or excessive diuretic therapy, administration of nephrotoxic drugs/contrast agents, or development of HRS[2,3]. The probability of the occurrence of HRS in patients with cirrhosis and ascites at 1 and 5 years is 18% and 39%, respectively, with mortality approaching 100% in type I HRS without specific therapy. The median survival time in these patients without liver transplantation was only 12 d after diagnosis in one study[9]. However, this seems to have improved with terlipressin and albumin therapy[10]. The development of ARF in patients with cirrhosis has significant prognostic importance. In patients with cirrhosis admitted to hospital with acute upper gastrointestinal hemorrhage, development of ARF forms an independent predictive factor for death[11,12].

PATHOPHYSIOLOGY OF RENAL FAILURE IN LIVER DISEASE

The mechanism underlying the development of ARF in advanced liver disease and cirrhosis is complex and includes interactions between changes in the systemic arterial circulation, portal hypertension, activation of vasoconstrictors and suppression of vasodilatory factors acting on the renal circulation[1,3,13]. The pathophysiology of functional renal failure in ALF is similar to that in cirrhosis[6,14], and patients with ALF may develop portal hypertension, but to a lesser degree than in those with cirrhosis[6]. The common pathway of renal dysfunction is the development of intense systemic arterial vasodilation, which follows increased release of endogenous vasodilators, especially nitric oxide, which escapes from the splanchnic to the systemic circulation through portosystemic shunts[1,13-15]. The systemic vasodilation leads to a reduction in systemic vascular resistance (SVR) and consequent high cardiac output and hyperdynamic circulation. However, the increase in cardiac output may be inadequate to compensate for the drop in SVR, especially in ALF, which results in hypotension with mean arterial pressure (MAP) commonly falling to 60-70 mmHg, which is on the pressure-dependent part of the autoregulatory curve of renal blood flow (RBF)[6,16]. In healthy individuals, autoregulation of RBF occurs until the renal perfusion pressure falls below 60-70 mmHg. Altered renal vascular autoregulation, as seen in sepsis, may also be present in the hyperdynamic circulatory failure of ALF, making RBF directly dependent on blood pressure[17]. In some patients with cirrhosis, especially alcoholics, the presence of cardiomyopathy and heart failure may further render them susceptible to renal compromise secondary to hypoperfusion[18].

The normal homeostatic response to vasodilation is activation of several neurohumoral mechanisms, such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and arginine-vasopressin (AVP) which leads to intense vasoconstriction and salt and water retention, in an attempt to maintain blood pressure and perfusion of vital organs[2,5,14,17]. Other vasoconstrictors, such as eicosanoids, endothelins, thromboxane A2 and leukotrienes may further exacerbate this[6,13,14,19].

RBF is kept within normal limits in the early stage of the liver disease, due to the release of certain local vasodilators such as prostaglandins. However, in situations in which circulatory volume is acutely diminished, as in gastrointestinal hemorrhage, renal hypoperfusion and subsequent pre-renal azotemia may occur. As the liver disease progresses, there is extreme vasoconstriction of the renal vascular bed that predisposes the kidneys to development of HRS[2,20]. The presence of tense ascites may further impair renal perfusion. The continuing vasoconstriction and raised vascular resistance results in contraction of the mesangium, with a reduction in glomerular surface area, which leads to acute tubular necrosis (ATN)[21].

CAUSES OF ACUTE RENAL FAILURE IN LIVER DISEASE

Pre-renal

Patients with advanced liver disease are susceptible to pre-renal azotemia, secondary to the development of relative hypovolemia and reduced effective central blood volume. The initial event is development of portal hypertension, which then leads to splanchnic and systemic vasodilatation mediated by NO and other vasodilators. Vasodilatation seems to be the main mechanism, however, underfilling has also been suggested, which is explained by fluid sequestration in the peritoneal cavity[22-24]. True hypovolemia can further exacerbate renal dysfunction in these patients. It can be induced by gastrointestinal tract hemorrhage from varices, peptic ulcers, gastropathy or other sources, excessive diuresis, vomiting and diarrhea, or can be aggravated by large volume paracentesis without intravascular volume replacement[3,11,13]. Bacterial infections and the use of nonsteroidal anti-inflammatory drugs can also precipitate pre-renal azotemia in these patients[3,25]. Patients with ALF and cirrhosis are abnormally susceptible to infection. Hemodynamic abnormalities induced by cytokines and vasodilating substances, such as NO in spontaneous bacterial peritonitis, play an important role in the pathogenesis of renal dysfunction. Additionally, development of septic shock further impairs renal function[25,26].

Intrinsic renal

Intrinsic renal disease can either complicate acute liver diseases as a result of exposure to certain drugs, toxins and infections, or be a part of chronic liver disease. The former usually is tubular interstitial in nature and presents as ARF, while the latter predominantly leads to glomerulopathy and is characterized by stable kidney disease. The causes of intrinsic renal involvement in liver diseases are numerous and are beyond the scope of this review. This review will mainly concentrate on acute tubular necrosis (ATN) and HRS, with other causes listed in the Table 1.

ATN

Direct cellular toxicity with ATN and hepatocyte necrosis have been observed in paracetamol intoxication[16]. Despite the nephrotoxic potential of this drug, functional renal failure is also seen secondary to ALF. Renal failure rarely

occurs in the absence of liver failure[7]. Depletion of glutathione is believed to be the cause of both ARF and ALF[36]. Aspirin is another analgesic drug that can cause dose-related liver damage and renal failure in susceptible patients. Of special interest is the association of aspirin, used to treat symptoms of influenza or varicella, with Reye's syndrome[27,37]. The mechanism of renal damage is due to cyclooxygenase inhibition thereby preventing the production of vasodilatory prostaglandins.

ATN with acute renal insufficiency in patients with stable liver disease often follows insults such as hypovolemic shock, major surgical procedures and use of nephrotoxic drugs or contrast agents, infection or sepsis. The functional renal abnormalities associated with advanced liver disease and cirrhosis increase the susceptibility of the kidneys to the development of ATN. These renal abnormalities may either be ischemic or toxic in origin. The mechanism of renal failure is similar in both, and results from a reduction in glomerular filtration rate (GFR) due to impaired glomerular capillary pressure, disrupted integrity of tubular epithelium, and tubular obstruction from casts composed of detached epithelial cells, cellular debris and pigments (hemoglobin and myoglobin)[38]. It should be noted that all causes of pre-renal azotemia might lead to ischemic tubular injury if left untreated[21,39].

The association of obstructive jaundice and ARF is well-established. Susceptibility to renal failure in obstructive jaundice is a combination of cardiovascular instability due to defective vascular reactivity and blunted myocardial contractile response as a result of the deleterious effects of bile constituents. Furthermore, the natriuretic effects of bile acids can cause volume depletion and exaggerate the effective arterial underfilling. However, there is a direct nephrotoxicity of biliary products at very high levels of bilirubin (> 30 mg/dL) in both children and adults[40,41].

Contrast medium is a well-known precipitant of renal failure in hospitalized patients, particularly in the presence of predisposing conditions such as reduced effective blood volume, dehydration and diabetes mellitus. Cirrhosis has been considered a potential predisposing factor. However, a prospective study in euvolemic patients with cirrhosis has shown that administration of contrast medium is not associated with adverse effects on renal function, which suggests that cirrhosis per se should not be considered a risk factor for contrast media nephrotoxicity[42,43]. However, it may play a role in septic cirrhosis, or in patients who have bleeding or who have undergone transarterial embolization for hepatocellular carcinoma.

Table 1 Intrinsic kidney involvement in liver diseases

Tubulo-interstitial involvement
1 Drugs[7] (paracetamol, aspirin, carbon tetrachloride, halogenated hydrocarbons, immunosuppressant agents)
2 Toxins[28-35] (Galerina family of mushrooms, hemoglobin, myoglobin, bilirubin, contrast agents)
3 Infections (leptospirosis, malaria, hepatitis)
4 Hypersensitivity reactions (sulphonamides, salicylates, *etc.*)
Glomerular involvement
1 Drugs[7] (carbon tetrachloride)
2 Hepatitis[28-35] A, B, C
3 Type Ⅱ mixed cryoglobulinemia[28-35]
4 IgA nephropathy[28-35] (alcoholic cirrhosis, HCV cirrhosis)
5 Others (sickle cell disease, hemochromatosis, acute fatty liver and toxemia of pregnancy)
Vascular
1 Vasculitis
2 Toxemia of pregnancy and HELLP syndrome

HRS

HRS is a unique form of functional renal failure that often complicates advanced liver disease, hepatic failure or portal hypertension[3,9,20]. The incidence of HRS in patients with cirrhosis hospitalized for ascites is about 10%. The syndrome is characterized by intense intrarenal vasoconstriction in the presence of vasodilation of systemic and splanchnic circulation, which triggers a reduction in peripheral vascular resistance and a decrease in effective systemic circulatory volume, despite an overall expanded total extracellular fluid volume. The majority of patients have clinical evidence of advanced cirrhosis[20]. However, HRS may occur in patients with fulminant viral and alcoholic hepatitis[36]. Two patterns of HRS can be identified.

Type 1 HRS is characterized by a rapidly progressive reduction of renal function, defined as either doubling of the initial serum creatinine to > 2.5 mg/dL or a 50% reduction in GFR to < 20 mL/min over a 2-wk period. Precipitating factors include spontaneous bacterial peritonitis (SBP), major surgical procedures, and acute alcoholic hepatitis. It follows a fulminant course with development of oliguria, encephalopathy, and marked hyperbilirubinemia, and is associated with very poor prognosis, with death occurring within 1 mo after presentation[27,36].

Type 2 HRS is characterized by a more benign course, with a stable reduction in GFR over weeks to months, accompanying diuretic-resistant ascites and avid sodium retention[36]. The pathogenesis of HRS is incompletely understood. It may be the result of an imbalance between renal vasodilators and vasoconstrictors, with the latter predominating. This interplay between the intrarenal mechanisms is triggered by one of the above-mentioned precipitating factors, which exacerbate the previously diminished cardiac and renal function[14,20].

The diagnostic criteria of HRS as proposed by the International Ascites Club are listed in Table 2[44]. Only the major criteria are necessary for the diagnosis of HRS, while the minor criteria are supportive. The diagnosis of HRS is one of exclusion and depends mainly on the level of serum creatinine, despite the fact it does not provide an accurate reflection of GFR in patients with cirrhosis[8]. Patients with cirrhosis with serum creatinine > 1.5 mg/dL have a GFR (estimated by inulin clearance) of < 30 mL/min, which represents one quarter of the normal GFR for healthy subjects of the same age[45]. HRS is a form of functional renal failure, therefore, the

Table 2 Diagnostic criteria of HRS

Major criteria
1 Chronic or acute liver disease with advanced liver failure and portal hypertension
2 Low GFR, as indicated by a serum creatinine of > 1.5 mg/dL or a 24-h creatinine clearance < 40 mL/min
3 Exclusion of shock, ongoing bacterial infection, volume depletion, and the use of nephrotoxic drugs
4 No improvement in renal function despite stopping diuretics and volume repletion with 1.5 L of saline
5 No proteinuria or ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Minor criteria[1]
1 Urine volume lower than 500 mg/day
2. Urine sodium lower than 10 mEq/L
3 Urine osmolality > plasma osmolality
4 Urine blood cells < 50 per high-power field
5 Serum sodium concentration lower than 130 mEq/L

[1]Only major criteria are necessary for the diagnosis of hepatorenal syndrome.

characteristics of urine are those of pre-renal azotemia with oliguria, low sodium concentration, and increased osmolality and urine to plasma ratio. These parameters are not considered essential for the diagnosis of HRS because they may overlap with different types of renal failure[44,45].

DIFFERENTIAL DIAGNOSIS OF ARF IN LIVER DISEASE

The differential diagnosis of ARF in advanced liver disease includes pre-renal failure, intrinsic renal failure and HRS (Table 3). The diagnostic evaluation relies upon clinical and laboratory data, including examination of urinary sediment and urinary chemistry, as well as appropriate ultrasonographic and radiological investigations[3,14,20]. Renal biopsy generally is not necessary for the diagnosis of ARF in liver disease, but is useful in excluding an intrinsic renal disorder[3]. A history of gastrointestinal hemorrhage, vomiting or diarrhea, exposure to nephrotoxic medication, or features suggestive of sepsis may provide important diagnostic information. Arterial hypertension, which is an unexpected finding in patients with cirrhosis, suggests glomerulonephritis[46]. The course of renal response to fluid challenge or vasoconstrictor therapy can also help differentiate causes of acute azotemia in liver disease. Rapid improvement in renal function denotes pre-renal failure, whereas mild or no improvement represents ATN or HRS[39,44]. Vasoconstrictor agents such as terlipressin or noradrenalin can sometimes be used to differentiate HRS and ATN, with improvement of GFR in favor of HRS[47,48]. Urine indices such as osmolality, sodium concentration, urine:plasma osmolality ratio (U/Posm) and urine:plasma creatinine ratio (U/Pcreat), are useful theoretical tools for differential diagnosis of the three principal causes of ARF in liver disease. However, in reality apart from urinary sediments these are often not clear cut.

Duplex Doppler ultrasonography, is a sensitive method of assessing intrarenal hemodynamics in patients with stable cirrhosis and ascites, in whom the renal artery resistive index is significantly increased and correlated with GFR and plasma renin activity[49]. However, this method is only useful in stable cirrhosis and may not be applied to acute situations.

Table 3 Differential diagnosis of ARF in advanced liver disease

	Prerenal failure	Intrinsic renal failure	HRS
Urine sodium	< 10	> 30	< 10
U/Pcreat	> 30:1	< 20:1	> 30:1
U/Posm	UO > PO	UO = PO	UO > PO
Urine sediment	Normal	Casts, cellular debris	Unremarkable
History disease	Profound volume	Volume contraction	Advanced liver disease
Clinical course (renal response)	Contraction	Nephrotoxic agent sepsis	Tence ascites
Fluid challenge	+	-	-
Vasoconstriction	±	-	+
Ultrasound	Elevated resitive index	Elevated resitive index	Elevated resitive index

MANAGEMENT OF ARF IN LIVER DISEASE

Management of ARF in liver disease should follow the same general principles as for the management of renal failure of any etiology, as well as specific measures for the liver disease. Combined ARF and ALF should ideally be managed in an intensive care or high-dependency setting. Initial management comprises correction of life-threatening abnormalities such as hyperkalemia, hypoglycemia, severe blood gas abnormalities, gross fluid overload and coagulation disorders, which may lead to bleeding and worsening renal function[50]. Although bleeding problems in patients with chronic liver failure are much less than previously thought, as a result of normal thrombin generation, renal failure superimposed on liver failure may have a negative impact on bleeding diathesis and worsening of hemorrhage[51].

Potential nephrotoxic drugs should be discontinued if possible, diuretic therapy interrupted, and infusion of crystalloid or colloid solutions commenced, based on clinical assessment and hemodynamic monitoring. In ALF complicated by intracranial hypertension, in addition to general measures to treat cerebral edema, early continuous renal replacement therapy (CRRT) may be considered, especially when patients are oligo-anuric and are taking mannitol[5,6].

In patients with chronic liver disease, management of ARF must focus on pre-renal failure, HRS and ATN. Upper gastrointestinal hemorrhage needs transfusion of plasma expanders and packed red blood cells, while measures are being taken to identify and treat the bleeding focus[12]. Intestinal and renal fluid losses should be replaced with appropriate fluid. Evidence of sepsis should be meticulously sought and a non-nephrotoxic broad-spectrum antibiotic regimen commenced, regardless of the etiology of sepsis. Current literature does not support the role of low-dose dopamine in the prevention and treatment of sepsis-induced renal vasoconstriction and

failure[52]. Vasopressin and terlipressin provide adequate splanchnic vasoconstriction and have been used not only in patients with cirrhosis and HRS, but also in sepsis in resistant cases[53].

Many different therapeutic approaches have been proposed for the management of HRS[2,13,27,38]. Unfortunately, most treatment measures result in only transient beneficial effects on renal function, and are not consistently associated with improvement in patient survival. Liver transplantation remains the definitive treatment for HRS, but is associated with higher hospital mortality compared to those without HRS who are treated with transplantation[54]. Thus, every attempt should be made to prevent this severe complication or reverse it when managing patients with cirrhosis and ascites. In recent years, new treatment strategies such as the use of vasoconstrictor drugs, along with plasma volume expansion, or insertion of TIPS, have shown some promise[20]. These treatments may prolong survival time and, therefore, act as a bridge to liver transplantation in these patients. Vasoconstrictors used for HRS include vasopressin analogues (ornipressin and terlipressin), somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenalin)[20]. In type 1 HRS terlipressin in combination with albumin has shown to result in greater improvement in renal function compared to terlipressin alone[10,53]. Pharmacological treatment, when combined with interventional techniques, such as transjugular intrahepatic portosystemic shunt (TIPS), may further improve renal function in HRS[27,55]. However, TIPS is frequently associated with significant side effects, particularly hepatic encephalopathy and impairment of liver function, and its role in the management of HRS needs to be established by prospective, controlled investigations[56].

The molecular adsorbent recirculating system (MARS) has been used in the treatment of acute decompensation of chronic liver disease (ADCLF), ALF and HRS[57]. This liver support system utilizes either intermittent (6-8 h daily) or continuous hemodialysis with dialysate enriched with 20% human serum albumin as a means to remove albumin-bound toxins (bilirubin, bile acids, fatty acids, tryptophan, aromatic amino acids, and copper). The first randomized trial of MARS evaluated 13 ADCLF patients with type 1 HRS. Five patients treated with hemodiafiltration alone died within 7 d, whereas three of eight patients treated with MARS were alive at 7 d, and two of eight were alive at 30 d[58]. Another recent randomized control trial, which included 24 patients with ADCLF, showed improvement in hyperbilirubinemia and hepatic encephalopathy and 30-d survival in patients treated with MARS. There was also improvement in renal function in the MARS group[59]. Until now, MARS has shown no benefit in improving survival in acute exacerbations of chronic liver failure. Likewise, MARS in the context of ALF has not been studied in control trials.

CRRT

Theoretically, the indications for CRRT in advanced liver disease and renal failure should be similar to those for general population. However, in view of the underlying disease, renal support should only be provided to those with a clear goal of hepatic management and a potential positive outcome i.e., the possibility of hepatic recovery or liver transplantation[60,61]. Measures such as volume expansion with albumin and the use of terlipressin should be tried before considering RRT. In fulminant hepatic failure (FHF), CRRT has become a major part of the routine management. Although there are no randomized trials to prove its efficacy, it can be assumed that it has contributed in part to the improvement in mortality. The continuous form provides greater hemodynamic, and more importantly, greater intracranial pressure ICP stability than the intermittent forms[62]. Continuous techniques (hemofiltration/hemodiafiltration) are preferred since they are associated with greater cardiovascular stability and allow gradual fluid removal, which can be adapted to actual needs and the infusion volume required for drug therapy and nutritional support[61].

PREVENTION OF RENAL FAILURE IN ADVANCED LIVER DISEASE

Two different strategies can be used to prevent HRS. The first is to perform liver transplantation in patients with cirrhosis and ascites before HRS develops. The identification of factors associated with a high risk of developing HRS and the use of duplex Doppler ultrasonography to assess the renal artery resistive index in the follow-up of these patients may be useful for this purpose[9,24,49]. The second strategy is to prevent the development of renal impairment in patients by avoiding the precipitating factors i.e., prompt management of bleeding and infection. A recent study has indicated that the development of HRS in patients with SBP can be effectively prevented by the addition of albumin to antibiotic (cefotaxime) therapy (1.5 g/kg human albumin intravenously at the time of diagnosis of the infection and 1 g/kg intravenously 48 h later). The proportion of patients who developed HRS and the in-hospital mortality was significantly lower in the cefotaxime-plus-albumin group that in the cefotaxime alone[63]. The beneficial effect of albumin is probably related to its ability to prevent circulatory dysfunction and subsequent activation of vasoconstrictor systems that occur during infection[63].

ARF POST LIVER RESECTION AND LIVER TRANSPLANTATION

Liver transplantation is the optimal treatment for patients with end-stage liver disease and ALF. The immediate outcome of orthotopic liver transplantation (OLT) is dependent on several factors, including pretransplant renal function and hemodynamic conditions in the operative and postoperative periods[63]. The prevalence of renal insufficiency in patients before transplantation varies from 10% to 20%, although many of these patients may have HRS, which is potentially a reversible condition.

Pretransplant renal dysfunction is a poor prognostic marker[64]. The reason for the poorer prognosis of these patients may be related to the persistence of the hyperdynamic circulation after liver transplantation, and to the fact that these patients seem to be more susceptible to damage from immunotherapy with cyclosporine or tacrolimus[65]. Additionally, pretransplant renal failure increases the incidence of postoperative sepsis, the need for pre- and postoperative dialysis, the number of days spend in the intensive care unit, and short-term graft and patient survival rates[64,66]. Renal failure is a frequent complication after OLT. It is usually acute, appears early after transplantation, and has an unfavorable effect on prognosis of liver transplant patients. The reported incidence ranges from 12% to 61%, according to the criteria used for defining ARF (serum creatinine ranging from 1.5 to 3 mg/dL or higher)[66,67]. Post-transplant ARF is usually caused by ATN due to perioperative complications (circulatory instability, duration), sepsis, repeated rejection, calcineurin-mediated renal vasoconstriction or nephrotoxic drugs (e.g., aminoglycosides and amphotericin B).

Prevention of renal failure after liver transplantation is not easy. The benefit of RRT with continuous venovenous hemodialysis before and after liver transplantation has been established[68]. Administration of aprotinin, an antifibrinolytic agent may be of benefit in the prevention of renal failure in adult patients undergoing OLT, by reducing intraoperative blood loss. Despite its potential nephrotoxic side effects, the administration of regular doses of aprotinin does not lead to a higher incidence of renal failure in these patients[69].

Treatment of HRS prior to OLT could also be beneficial for the prevention of ARF[63,66]. Finally, a delay in the introduction of nephrotoxic immunosuppresive drugs could be helpful in the prevention of post-transplant ARF, especially in high-risk patients.

CONCLUSION

Acute renal dysfunction is common in patients with acute and chronic liver disease. The presence of renal failure in this group of patients significantly affects mortality. Several advances have occurred in the management of this complication in the last decade. Improvement in the management of ARF in ALF is reflected in our better understanding of the disease process and better hemodynamic and renal replacement support. In advanced liver disease complicated by liver failure, terlipressin and early formation of TIPS have shown some promise. The role of MARS, bioartificial liver support, high-volume hemofiltration, and therapeutic plasma exchange, are still unclear and need further evaluation. Finally, as liver transplant is the definitive treatment, further education to increase the organ donation pool may be the best way forward.

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