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Review of literature: Renal abnormalities in liver disease

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Abstract---Renal failure is a common complication of liver cirrhosis and of utmost clinical and prognostic relevance. Patients with cirrhosis are more prone to developing acute kidney injury than the non-cirrhotic population. The differential diagnosis of renal dysfunction in advanced liver disease includes pre-renal failure, intrinsic renal failure and hepatorenal syndrome. Hepatorenal syndrome is a complication of advanced cirrhosis characterized by an abrupt deterioration in renal function. In cirrhosis with ascites, hepatorenal syndrome is a specific prerenal dysfunction. It is unresponsive to fluid volume expansion and is associated with an extremely poor prognosis. An accurate assessment of renal function is recommended in all patients with cirrhosis. Liver transplantation remains the definitive treatment for hepatorenal syndrome, but new treatment strategies can be utilized as a bridge to transplantation. This review provides an update on our present understanding of the underlying pathophysiological mechanisms involved, diagnostic criteria, different treatment approaches and strategies to prevent Hepatorenal Syndrome.

Keywords---cirrhosis, hepatorenal syndrome, ascites, hypovolemia, pre-renal azotemia, acute tubular necrosis, liver transplantation.

Introduction

Renal function is an important indicator of the state of health of kidney. The impairment in renal function of varying severity, is common in patients with

liver diseases. The aim of treatment of renal failure in the patients suffering from chronic liver disease is an improvement of kidney function and a bridging to liver transplantation. One of the indicators of decompensation and poor prognosis in patients with cirrhosis is Ascites. There are different causes of renal dysfunction in patients with Liver diseases, most common ones being circulatory dysfunction due to bacterial infection, hypovolemia secondary to gastrointestinal bleeding, paracentesis or diuretic use, contrast or drug induced, chronic kidney disease and Hepatorenal syndrome. HRS is a functional type of renal failure found in patients with advanced cirrhosis and ascites.

History

The first description of disturbances in renal function in chronic liver diseases was made by Frerichs and Flint in two independent reports from the late nineteenth century(1). These reports described the development of oliguria in patients with chronic liver disease in the absence of proteinuria and with a normal renal histology, and proposed the first pathophysiologic interpretation of hepatorenal syndrome by linking the abnormalities of renal function to the disturbances present in the systemic circulation. The coexistence of renal impairment and liver disease has even been mentioned by Hippocrates(2); Helwig and Schutz introduced the term hepatorenal syndrome in 1932 when they described a patient with renal failure and biliary tract disease(3). The detailed clinical description of HRS, however, was not made until the 1950s in studies by Sherlock, Papper, and Vessin.

Renal Dysfunction in Liver Disease

The mechanism underlying the development of renal dysfunction 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.

Patients with advanced liver disease are susceptible to prerenal failure primarily due to disturbances in circulatory function- mainly, a reduction in systemic vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension⁽⁴⁾. The cause of this arterial vasodilatation is increased production or activity of vasodilator factors (particularly nitric oxide, carbon monoxide, and endogenous cannabinoids).

Another factor further exacerbating renal dysfunction in these patients is true hypovolemia, which can be induced by gastrointestinal tract haemorrhage from varices; peptic ulcers or gastropathy; excessive diuresis; vomiting and diarrhoea; or can be aggravated by large volume paracentesis without intravascular volume replacement. Bacterial infections (eg. spontaneous bacterial peritonitis) and the use of nonsteroidal anti-inflammatory drugs can also precipitate pre-renal failure in these patients. Development of septic shock is another possible event which may further impair renal function.

Sodium Retention and Ascites/Edema

It is the first manifestation of renal impairment in cirrhosis. The total amount of sodium retained is dependent on the balance between sodium intake and excretion. Patients may develop ascites or edema when sodium intake is increased (high sodium diet or administration of intravenous saline solution) or when they are treated with drugs that increase sodium reabsorption, (such as mineralocorticoids or NSAIDs.)

The underlying mechanism responsible for renal sodium retention is an increased renal tubular reabsorption of sodium in the proximal and distal tubules⁽⁵⁾. This occurs even in the presence of a normal or only moderately reduced GFR. The two main sodium retaining systems responsible are the renin- angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). These are activated as a homeostatic response to circulatory dysfunction.

Solute-Free Water Retention and Dilutional Hyponatremia

Hyponatremia occurs in nearly half of patients in hospital with cirrhosis and ascites, and is due to the excessive retention of solute-free water which results from the kidney's inability to excrete it normally. Pathogenesis of solute-free water retention in cirrhosis seems to be related to three events: Reduced delivery of filtrate to the ascending limb of the loop of Henle; a reduced renal synthesis of prostaglandins; and an increased secretion of anti-diuretic hormone.

The morbidity and mortality associated with hyponatremia is largely attributable to central nervous system disturbances. Altered steroid and peptide hormones in cirrhotic patients may contribute to the development of hyponatremia encephalopathy, symptoms of which overlap with hepatic encephalopathy and uremia⁽⁶⁾. The appearance of hyponatraemia in cirrhotic patients, long regarded as a poor prognostic sign, is now identified as a marker of unrecognized underlying impaired renal function.

Renal Vasoconstriction

Renal vasoconstriction leading to decreased renal perfusion is the renal functional abnormality that develops last in patients with cirrhosis and ascites. It is the consequence of the extreme underfilling of the systemic arterial circulation due to marked vasodilatation of the splanchnic circulation, which activates homeostatic vasoconstrictor systems, whose effect on the kidney vasculature cannot be counterbalanced by either renal or systemic vasodilators⁽⁷⁾.

Renal vasoconstriction predisposes to the development of hepatorenal syndrome (HRS).

Types of Renal Failure in Patients with Cirrhosis

Hypovolemia-Induced Renal Failure

Hypovolemia is usually due to gastrointestinal hemorrhage or to fluid losses-either renal losses because of excessive diuretic therapy; or gastrointestinal losses

as a result of diarrhea from excessive lactulose administration or gastrointestinal infection. Renal failure occurs soon after the onset of hypovolemia.

Parenchymal Renal Disease

Parenchymal renal disease should be suspected as a cause of renal failure when proteinuria (>500 mg of protein/day), hematuria (>50 red cells/high-power field), or both are present and ideally should be confirmed by renal biopsy, if this procedure is not contraindicated. The presence of renal tubular epithelial cells in the urine sediment favours the diagnosis of acute tubular necrosis.

Drug-Induced Renal Failure

Current or recent treatment with nonsteroidal anti-inflammatory drugs or aminoglycosides suggests drug-induced renal failure.

Hepatorenal Syndrome

Hepatorenal syndrome is an uncommon but potentially fatal complication of decompensated cirrhosis. It is a unique form of functional renal failure that often complicates advanced liver disease, hepatic failure or portal hypertension. It is characterized by intense constriction of the renal arterial vasculature with resulting oliguria and avid sodium retention.

The definition of HRS as proposed by International Ascites Club is,

“Hepatorenal syndrome is a clinical condition that develops in patients with chronic liver disease and advanced hepatic failure and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney there is marked renal vasoconstriction that results in low GFR. There is also vasoconstriction in other vascular territories such as the muscle, spleen and brain. In the splanchnic circulation, there is an intense arteriolar vasodilatation that results in reduction of total systemic vascular resistance and arterial hypotension. A similar syndrome can also develop in the setting of acute liver failure.”⁽⁸⁾

Hepatorenal syndrome may occur spontaneously or in response to some insult such as infection, haemorrhage, or overly vigorous diuresis. The renal circulation in hepatorenal syndrome demonstrates several abnormalities:

- reduction of renal blood flow and glomerular filtration;
- vasoconstriction involving the branches of the main renal artery and other smaller arteries;
- cortical ischemia and instability.

There are two patterns of hepatorenal syndrome(HRS):

Type I HRS is characterized by a rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher

than 2.5 mg/dl or a 50% reduction of the initial 24 hour creatinine clearance to a level lower than 20 ml/min in less than 2 weeks.

The dominant features of type I HRS are marked renal failure with oliguria or anuria and increased serum levels of urea and creatinine. This type of HRS is frequently seen in patients with alcoholic cirrhosis, especially when associated with alcoholic hepatitis, but it occurs in non-alcoholic cirrhosis as well. Precipitating factors include spontaneous bacterial peritonitis (SBP) and major surgical procedures.

Most patients show signs of severe liver failure with marked hyperbilirubinemia, low prothrombin activity, and encephalopathy. It follows a fulminant course with development of oliguria and is associated with very poor prognosis, with death occurring within 1 month after presentation⁽⁴⁾.

In contrast to type I, type II HRS is characterized by less severe and stable reduction of GFR that does not meet the criteria proposed for type I. Patients are usually in better clinical condition than those with type I HRS, and their survival expectancy is markedly longer. The clinical picture is one of moderate stable renal disease in a patient with diuretic-resistant ascites due to the combination of intense sodium retention, reduced GFR, and marked stimulation of antinatriuretic systems.

The diagnosis of HRS is one of exclusion and depends mainly on the level of serum creatinine, despite the fact that it does not provide an accurate reflection of GFR in patients with cirrhosis.

Pathogenesis of Hepatorenal Syndrome

Hepatorenal syndrome is characterised by functional renal vasoconstriction that leads to a severe reduction in GFR with minimal renal histologic abnormalities. Function can be restored following correction of portal hypertension by liver transplantation or even when the kidneys are removed and transplanted into a non-cirrhotic recipient⁽⁹⁾. The initial abnormality in hepatorenal syndrome is peripheral and splanchnic arterial vasodilatation triggered by portal hypertension. This vasodilatation initiates adaptive responses that stimulate renal vasoconstriction and renal sodium and water retention.

Various mechanisms which contribute to the pathogenesis of HRS are:

1. Renin-Angiotensin-Aldosterone system (RAAS)

The activation of RAAS is particularly intense in patients with hepatorenal syndrome. Plasma aldosterone levels are increased in most cirrhotic patients with ascites and marked sodium retention. This is due to a stimulation of aldosterone secretion and not due to impaired degradation as the hepatic clearance of aldosterone is normal or only slightly reduced in these patients. It has also been suggested that cirrhotic patients may have an increased tubular sensitivity to aldosterone. This explains the renal sodium retention even in patients with normal levels of aldosterone. Hence spironolactone, a specific aldosterone antagonist is able to reverse sodium

retention and cause natriuresis in cirrhotics. Plasma renin activity is also often elevated in patients with decompensated cirrhosis⁽¹⁰⁾. The role of angiotensin II is shown by the improvement of renal function in patients with HRS achieved by the administration of vasopressin analogues ornipressin or terlipressin associated with albumin, which causes a marked suppression of RAAS activity.

2. Sympathetic Nervous System

Patients with hepatorenal syndrome have significantly higher plasma levels of norepinephrine than do patients without renal failure; and this correlates inversely with renal blood flow; suggesting that the sympathetic nervous system may participate in the renal vasoconstriction observed in patients with hepatorenal syndrome. Moreover, the circulating levels of neuropeptide Y, a neurotransmitter with a very potent vasoconstrictor action in the renal circulation released in the setting of a marked activation of the sympathetic nervous system, are increased in patients with hepatorenal syndrome but not in those with ascites without renal failure.

3. Prostaglandins

Patients with hepatorenal syndrome have lower urinary excretion of PGE₂ and PGI₂ than do patients with ascites without renal failure, which suggests that a reduced renal synthesis of vasodilator prostaglandins may play a role in the pathogenesis of HRS⁽⁹⁾. As prostaglandins are potent vasodilators in the systemic circulation, an increased systemic prostaglandin synthesis may contribute to arterial vasodilatation in cirrhosis. Moreover, a decrease in GFR and renal plasma flow by non steroidal anti-inflammatory drugs points towards a role of prostaglandin in maintaining normal renal perfusion. It has also been postulated that an imbalance between vasodilator and vasoconstrictor metabolites of arachidonic acid, with the latter dominating, contributes to irreversible vasoconstriction characterising HRS

4. Adenosine

Intrahepatic adenosine causes an increase in portal venous blood flow and triggers a hepatorenal reflex (to regulate sodium and water excretion) which by means of increasing sympathetic activity in the kidney, leads to a decrease in renal blood flow and GFR⁽¹¹⁾. This mechanism has been recently proposed which may lead to decreased renal perfusion and hepatorenal syndrome. Increased synthesis of adenosine may be accounted by tissue hypoxia due to advanced hepatic dysfunction.

5. Natriuretic Peptides

The plasma concentration of major natriuretic hormones, namely, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), is increased in patients with cirrhosis and ascites⁽⁹⁾. These high levels are due to enhanced cardiac release and not due to a reduced hepatic or systemic clearance. As these peptides have powerful effects on renal function (mainly vasodilator and natriuretic effects) and inhibit renin release, increased levels may act as a homeostatic mechanism to counteract the effects of anti-natriuretic and vasoconstrictor systems in the renal circulation. But the existence of increased plasma levels of ANP in cirrhosis, in the presence of renal sodium retention, indicates a renal resistance to the effects of ANP.

6. Nitric oxide

Nitric oxide (NO) is a powerful vasodilator agent released from vascular smooth muscle. It has been proposed to be an important effector responsible for splanchnic vasodilation in cirrhosis. NO plays a role in the regulation of glomerular microcirculation by modulating the arteriolar tone and the contractility of mesangial cells. It facilitates natriuresis in response to changes in renal perfusion pressure and regulates renin release. It was found in a study that NO increased significantly with progression of liver disease especially in the decompensated cirrhotic group⁽¹²⁾. This result supports that NO is important in the progression of cirrhosis. As a result, with an increase in NO with progression of the liver disease, especially in ascitic cirrhosis, renal tubular and glomerular functions are negatively affected.

7. Endothelin

The circulating levels of endothelin-1, an endothelial derived peptide with potent vasoconstrictor effect are also increased in cirrhosis probably due to an enhanced release of the peptide from the hepatic and/or splanchnic circulation. It has been proposed that the increased circulating levels and/or enhanced intrarenal production of endothelin may induce vasoconstriction of the renal circulation and play a role in the pathogenesis of hepatorenal syndrome.

8. Endotoxins

In cirrhotic patients the entire gastrointestinal tract becomes densely colonized with bacteria, presumably because of the patient's immunosuppressed status. Jaundice commonly observed in cirrhosis can promote reabsorption of endotoxin into the bloodstream. As the reticuloendothelial cells of the liver are likely to be compromised in advanced cirrhosis, absorbed endotoxin would not be completely destroyed by the hepatic Kupffer cells and would appear in the arterial circulation. The continuous reabsorption of endotoxin from the gastrointestinal tract into the circulation of patients with advanced cirrhosis leads to vasoconstriction of the renal microcirculation⁽¹³⁾. In summary, peripheral vasodilatation is the early event in the pathogenesis of fluid retention and hepatorenal syndrome. Following initial vasodilatation, maintenance of normal renal perfusion depends on a balance between vasodilatory and vasoconstricting factors. Hepatorenal syndrome represents an imbalance favouring vasoconstrictive over vasodilating factors, the consequences of which are a marked increase in renal vascular resistance, decrease in GFR, and avid sodium and water retention

Diagnostic Criteria for Hepatorenal Syndrome⁽¹⁴⁾

Major Criteria

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension
2. Low glomerular filtration rate as indicated by serum creatinine of $>1.5\text{mg/dl}$ or 24 hour creatinine clearance $<40\text{ml/min}$
3. Absence of treatment with nephrotoxic drugs, shock, infection or significant recent fluid losses

4. No sustained improvement in renal function after diuretic withdrawal and volume expansion with 1.5 L of isotonic saline
5. Proteinuria < 0.5 g per dL and no ultrasonographic evidence of obstruction or parenchymal renal disease

Additional Criteria

1. Urine volume <500 ml/day
2. Urine sodium <10mEq/L
3. Urine osmolality greater than plasma osmolality
4. Urine red blood cells <50 per high power field
5. Serum sodium concentration < 130mEq/L

Pseudo-Hepatorenal Syndrome

There are various conditions in which both liver and kidneys are affected, but in which the liver disease does not play an etiological role in the pathogenesis of renal failure. These conditions constitute the so-called “pseudo-hepatorenal syndrome”⁽¹⁵⁾.

Causes of Pseudo-Hepatorenal Syndrome

1. Congenital – Polycystic disease, sickle cell anaemia, congenital hepatic fibrosis, nephronophthisis
2. Toxic agents – Drugs: tetracycline, halothane, acetaminophen, sulphonamides, rifampicin, allopurinol, phenytoin, methoxyflurane, methotrexate (high dose); and other toxic agents: carbon tetrachloride poisoning in industrial workers, chloroform, arsenic, barium
3. Infections – Miliary tuberculosis, hepatitis B, hepatitis C, HIV, Schistosomiasis, septicaemia, yellow fever, leptospirosis
4. Connective tissue disorders- SLE, Sjogren's syndrome
5. Circulatory alterations – Shock, heart failure
6. Unknown aetiology – Amyloidosis, sarcoidosis,
7. Reye's syndrome

Treatment of Hepatorenal Syndrome

Many different therapeutic approaches have been proposed for the management of hepatorenal syndrome. 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 hepatorenal syndrome; recovery of renal function is typical after that. In patients with either type 1 or type 2 HRS, the prognosis is poor unless transplant can be achieved within a short period of time.

Transplantation in hepatorenal syndrome is associated with higher hospital mortality compared to those without HRS who are treated with transplantation⁽¹⁶⁾. 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 with preferential

effect on the splanchnic circulation(V1 receptor agonists), along with plasma volume expansion, or insertion of TIPS, have been used with promising results. These treatments may prolong survival time and, therefore, act as a bridge to liver transplantation in these patients. Vasoconstrictors used for hepatorenal syndrome include vasopressin analogues (ornipressin and terlipressin), somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenalin)⁽¹⁷⁾. In type 1 hepatorenal syndrome terlipressin in combination with albumin has shown to result in greater improvement in renal function compared to terlipressin alone⁽¹⁸⁾. Pharmacological treatment, when combined with interventional techniques, such as transjugular intrahepatic portosystemic shunt (TIPS), may further improve renal function in hepatorenal syndrome. However, TIPS is frequently associated with significant side effects, particularly hepatic encephalopathy and impairment of liver function⁽¹⁹⁾, and its role in the management of hepatorenal syndrome needs to be established by prospective, controlled investigations.

The molecular adsorbent recirculating system (MARS) has been used in the treatment of acute decompensation of chronic liver disease, acute liver failure and hepatorenal syndrome. 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)⁽²⁰⁾.

Evaluation of Patients With Cirrhosis and Renal Failure

Renal function should be routinely monitored in all patients with advanced cirrhosis, especially those with ascites. Patients who have ascites, particularly those with hyponatremia, bacterial infections, gastrointestinal bleeding, or severe sodium retention, are at high risk for renal failure, as are all patients hospitalized for acute decompensation of cirrhosis⁽²¹⁾. Other than blood urea nitrogen, serum creatinine and creatinine clearance, evaluation of renal function should also include

Serum electrolytes	Hyponatremia is common; potassium sparing diuretics should be discontinued to prevent hyperkalemia ;
Urine analysis	Significant proteinuria and urine sediment abnormalities usually indicate parenchymal renal disease
Renal ultrasonography	abnormal renal ultrasonograms indicate chronic parenchymal renal disease
Renal biopsy	helpful when parenchymal renal disease is suspected because of proteinuria, hematuria, or both and is also helpful in deciding on simultaneous kidney transplantation in candidates for liver transplantation. Renal biopsy is contraindicated if severe coagulation abnormalities are present.

The evaluation of patients with cirrhosis and renal failure should also include an assessment of liver function, as well as the exclusion of possible bacterial infections. The patient's medications should be reviewed, and diuretics should be discontinued, since these agents may either be the cause of renal failure or contribute to the impairment of renal function.

Differential Diagnosis of Renal Failure in Liver Disease

The differential diagnosis of renal dysfunction in advanced liver disease includes pre-renal failure, intrinsic renal failure and hepatorenal syndrome. The diagnostic evaluation relies upon clinical and laboratory data, including urine analysis, as well as ultrasonographic and radiological investigations. Renal biopsy generally is not necessary for the diagnosis of acute renal failure in liver disease, but is useful in excluding an intrinsic renal disorder⁽²²⁾. 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. Purpura, arthralgia, weakness, Raynaud's syndrome, or leg ulcers suggest cryoglobulinemia associated with hepatitis C. The presence of antibodies to hepatitis C virus and hepatitis C virus RNA, high concentrations of cryoglobulins, positive rheumatoid factor assays, and low concentrations of complement suggest hepatitis C virus-associated cryoglobulinemic glomerulonephritis⁽²³⁾.

Diagnostic information may be obtained from urine analysis. Pigmented granular casts are typical of ischemic and toxic acute renal failure and red cell casts of glomerulonephritis. Patients with renal azotemia due to acute or subacute glomerulonephritis have significant proteinuria (around 3 g/d). In contrast, proteinuria is absent or moderate in other causes of acute renal failure. 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 acute renal failure in liver disease.

Table I
Differentiation of HRS from Pre-Renal Azotemia and Acute Tubular Necrosis (ATN)^(24,25)

Differentiating		Pre-renal	Acute tubular
	HRS		
characteristic		azotemia	necrosis
History of	May/ may	Invariably	Present with fluid
precipitating event	not be	present; loss of	loss, shock, sepsis,
	present	fluids evident	or nephrotoxic
			drugs
Urine output	Oliguria	Oliguria	Oliguria, anuria
Urinary sediment	Absent	Hyaline casts	Granular casts,

			cellular debris
Urinary sodium (meq/l)	< 5	< 10	> 20
Urine to plasma osmolality ratio	> 1.5	> 1.5	1
Urine to plasma creatinine ratio	> 40	> 40	< 20
Response to plasma expansion	Absent	Good	Absent

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 in response to fluid challenge denotes pre-renal failure, whereas mild or no improvement represents acute tubular necrosis or hepatorenal syndrome. Vasoconstrictor agents such as terlipressin or noradrenalin can sometimes be used to differentiate between hepatorenal syndrome and acute tubular necrosis, with improvement of GFR in favour of hepatorenal syndrome⁽²⁶⁾. Duplex Doppler ultrasonography, is another sensitive method of assessing intrarenal hemodynamics in patients with cirrhosis and ascites, in whom the renal artery resistive index is significantly increased and correlates with GFR and plasma renin activity⁽²⁷⁾.

Prognosis of Renal Failure in Cirrhosis

The prognosis for patients with cirrhosis and renal failure is poor⁽²⁸⁾. The overall survival rate is approximately 50 % at 1 month and 20 % at 6 months .This extremely poor outcome is probably related to the combination of liver and renal failure, as well as to associated complications. However, survival rates can differ according to the type of renal failure. The hepatorenal syndrome is associated with the worst prognosis. The great majority of patients with hepatorenal syndrome have a poor short-term outcome unless they undergo liver transplantation. Mortality is higher with type 1 hepatorenal syndrome than with type 2 (median survival, 1 month vs. 6 months).

Prevention of Renal Failure in Advanced Liver Disease

Two different strategies can be used to prevent hepatorenal syndrome. The first is to perform liver transplantation in patients with cirrhosis and ascites before hepatorenal syndrome 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. 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.

Spontaneous bacterial peritonitis is a precipitating factor of HRS. SBP stimulates the production of the proinflammatory cytokine, tumor necrosis factor- α , which is known to induce vasorelaxant mechanisms in arteries⁽²⁹⁾. Thus, the SBP induced TNF-mediated activation of vasodilator mechanisms may enhance

preexisting systemic vasodilation (and arterial hypovolemia) and precipitate hepatorenal syndrome. It has been hypothesized that in patients with SBP, simultaneous intravenous administration of albumin and antibiotics could prevent the sepsis-induced decrease in effective arterial blood volume and resulting HRS.

A recent study has indicated that the development of hepatorenal syndrome 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 hr later)⁽³⁰⁾. The proportion of patients who developed HRS and the in-hospital mortality was significantly lower in the cefotaxime-plus-albumin group than in the cefotaxime alone. 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⁽³⁰⁾.

Other Renal Abnormalities in Cirrhosis

- **GLOMERULAR DISEASES**
In association with hepatitis B and C viruses and alcoholic liver disease
- **RENAL TUBULAR ACIDOSIS**
May occur in cirrhosis of different etiologies: primary biliary cirrhosis, autoimmune hepatitis and alcoholic cirrhosis
- **DRUG INDUCED RENAL DYSFUNCTION**
Especially with NSAIDs, aminoglycosides, diuretics or vasodilators
- **ACUTE TUBULAR NECROSIS**
Due to volume depletion as in sepsis or hypovolemic shock or due to nephrotoxic drugs

Summary

Patients with advanced liver disease are susceptible to prerenal failure primarily due to disturbances in circulatory function. Hypovolemia, bacterial infections, use of nonsteroidal anti-inflammatory drugs and septic shock are a few possible causes which may impair renal function. Sodium Retention and Ascites is the first manifestation of renal impairment in cirrhosis. Hyponatremia occurs in nearly half of the patients in hospital with cirrhosis and ascites. In patients with cirrhosis, renal failure can be hypovolemia-induced, Parenchymal renal disease, drug induced and a unique form of functional renal failure which is uncommon but potentially fatal complication of decompensated cirrhosis ie Hepatorenal syndrome. Transplantation in HRS is related with higher hospital mortality and hence every attempt should be made to prevent or reverse this severe complication when managing patients with cirrhosis and ascites.

Conclusion

The occurrence of renal abnormalities in patients with liver disease is a common event associated with a worsening of the prognosis. This requires special attention in keeping track of renal function in patients who have ascites, particularly those with hyponatremia, bacterial infections, gastrointestinal

bleeding or severe sodium retention . Liver transplantation is the first treatment option in patients with cirrhosis and ascites before hepatorenal syndrome develops . Secondly, the development of renal impairment can be prevented in patients by avoiding the precipitating factors ie prompt management of bleeding and infection . Many questions regarding diagnosis and treatment are still unanswered . Future study may help to refine diagnosis of renal failure and improve outcomes.

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