

The natural history and management of hepatorenal disorders: from pre-ascites to hepatorenal syndrome

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ABSTRACT – In cirrhosis, the natural history of hepatorenal disorders starts with a pre-ascitic stage and is followed by the development of ascites; hepatorenal syndrome (HRS) begins with compensated renal sodium retention, or pre-ascites. In pre-ascites, the renal sodium retaining tendency leads to 'overflowing' of total blood volume, with increased glomerular filtration rates (GFR), overcoming the renal sodium retaining tendency possibly due to renal accumulation of angiotensin II. As peripheral vasodilatation increases, the vascular capacity (in effect the arterial blood volume) becomes inadequately filled, GFR falls, compensatory vasoconstrictors rise, and the resulting renal sodium retention results in diuretic-responsive ascites formation. Increasing proximal reabsorption of sodium results in ascites refractory to diuretic therapy. Repeated abdominal paracentesis will not prevent insidious progression to HRS type II, nor to the precipitation of HRS type I. In contrast, liver transplantation, or transjugular intrahepatic hepatoportal stent shunt (TIPS) in refractory ascites, may prevent the onset of, or reverse, HRS. However, recent non-controlled studies indicate exciting possibilities of medical therapy reversing HRS.

KEY WORDS: abdominal paracentesis, ascites, cirrhosis, diuretics, hepatorenal syndrome, hyperkinetic circulation, liver transplantation, pre-ascites, transjugular intrahepatic hepatoportal shunt (TIPS), vasodilatation

Key Points

In compensated cirrhosis, pre-ascites may be defined as failure to reach sodium balance on a 200 mmol sodium diet within seven days

In pre-ascites, vasodilatation and hyperkinesis appear to be secondary to compensated sodium retention secondary to portal hypertension

The development of responsive ascites progressing to ascites refractory to distal and loop diuretics, is associated with increasing vasodilatation leading to increasing proximal tubular reabsorption of sodium

Hepatorenal syndrome now appears to be reversible by medical therapy

Introduction

The most severe hepatorenal disorders, refractory ascites and hepatorenal syndrome (HRS), account for more than 30% of referrals of cirrhotic patients for transplantation.¹ It is therefore important to understand the pathogenesis of the natural history of this complication of cirrhosis, and if possible prevent its development.

Pre-ascites (Fig 1a)

In patients with compensated cirrhosis which is free of ascites, it is possible to demonstrate abnormal renal handling of sodium. For example, when pre-ascitic cirrhotic patients are given a challenge of a 200 mmol sodium, high-salt diet for one week, they fail to achieve a sodium balance within that time, remaining in positive sodium balance, whereas normal healthy controls achieve a sodium balance within three to four days.² We found this the most physiological way of defining pre-ascites. In fact, if this high-salt diet is maintained, pre-ascitic patients do eventually achieve sodium balance after three to four weeks, along with a significant gain in weight, and without ultrasound evidence of ascites.³

The current theory explaining sodium retention in cirrhosis is known as the peripheral vasodilatation theory.⁴ This states that splanchnic vasodilatation, secondary to vasodilators such as nitric oxide, results in increased pooling of blood from the increased total blood volume within the splanchnic vascular bed. This results in hyperkinetic circulation with a decreased effective arterial blood volume, increased cardiac output, decreased systemic vascular resistance, decreasing renal blood flow (RBF), and glomerular filtration rate (GFR), with activation of the sodium-retaining systems, renin-angiotensin-aldosterone system (RAAS), and sympathetic nerve activity (SNA) initiating sodium retention. Although this explanation is clearly appropriate for the more advanced stages of ascites, does it explain pre-ascites, and the many patients with early ascites? In the upright position, pre-ascitic patients have no evidence of hyperkinetic circulation, but may have mild elevation of serum aldosterone levels and sodium retention.⁵ In contrast, when these patients

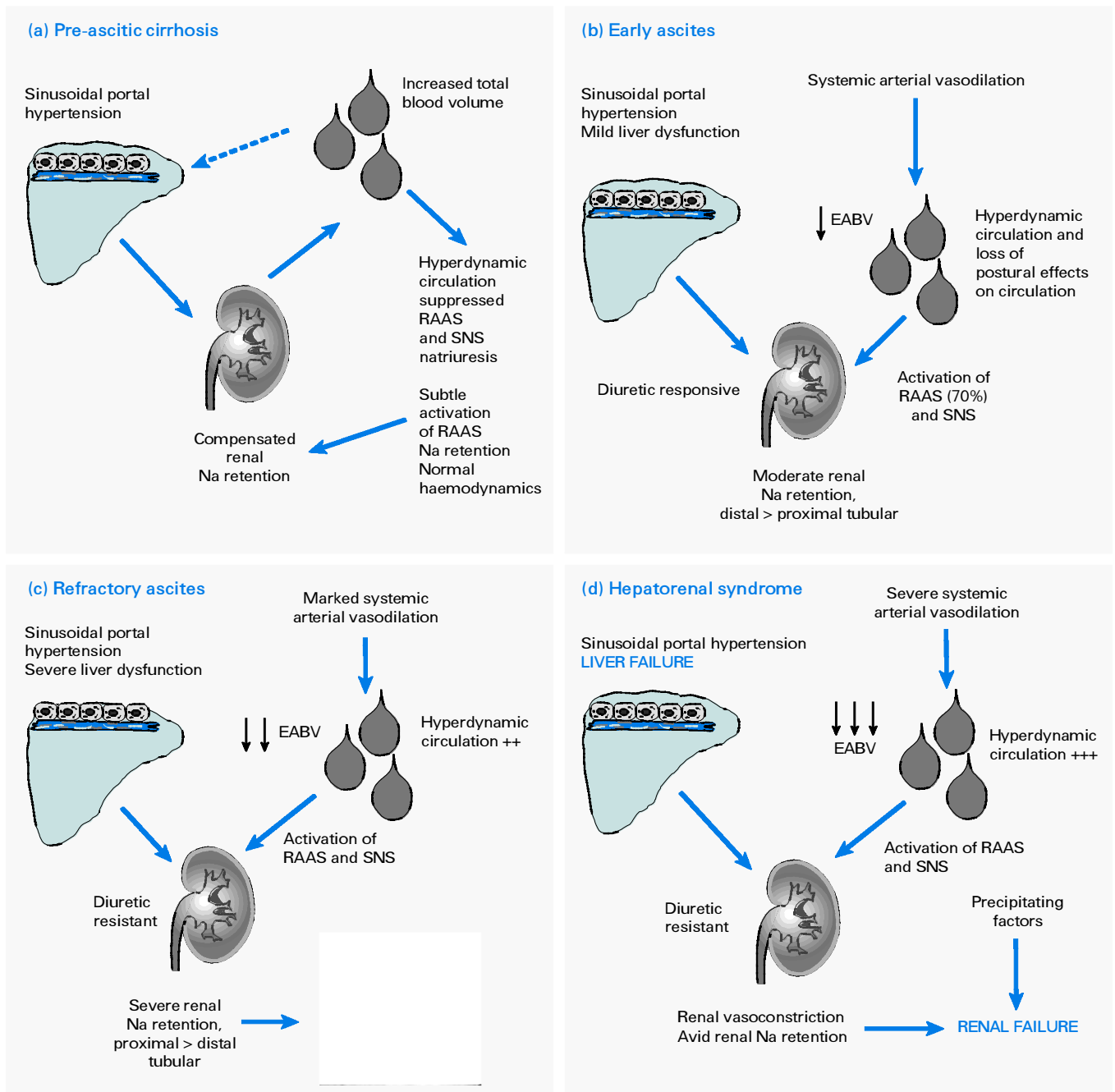


Fig 1. (a) Pre-ascitic cirrhosis. (b) Early ascites. (c) Refractory ascites. (d) Hepatorenal syndrome. RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system; EABV = effective arterial blood volume; Na = sodium.

assume the supine position, they do have evidence of hyperkinetic circulation.⁵ However, this is associated with suppression of RAAS and natriuresis. Thus, in contrast to the peripheral vasodilation theory,⁴ in pre-ascites vasodilatation appears to be secondary to positional change rather than the primary event, and is associated not with sodium retention but with natriuresis.

Additional findings in pre-ascitics in the supine position (Table 1) include elevation of GFR, or hyperfiltration,⁶ which, together with suppression of plasma renin activity (PRA), could be explained by volume expansion secondary to sodium reten-

tion and sympathetic hyperactivity.⁷ Indeed, in pre-ascites total blood volume is increased, together with extracellular volume and total body water. However, it is the critical volume, ie the effective arterial blood volume, supplying the kidney that impacts on renal function. It is impossible to measure this accurately. The closest approximation to this is measurement of the 'central blood volume' (CBV). This is essentially the intrathoracic blood volume, consisting of the four chambers of the heart, the great blood vessels and the pulmonary vasculature. This has been shown to be either decreased or normal, using a

Table 1. Characteristics of pre-ascites in cirrhosis

Definition

- 1 No evidence of ascites on abdominal ultrasound
- 2 Inability to achieve sodium balance on 200 mmol sodium diet within 7 days

Results of investigations

- 1 Normal or elevated GFR (hyperfiltrators)
- 2 Supine PRA and serum aldosterone: decreased
- 3 Sympathetic nerve activity (muscle): increased
- 4 Hyperkinetic circulation – supine position only
- 5 Total body water, extracellular fluid volume: increased
- 6 Total blood volume: increased
- 7 Central blood volume (CBV): normal or increased
- 8 Plasma ANF levels: increased
- 9 Plasma nitrous oxide (nitrite and nitrate) levels: increased

ANF = atrial natriuretic factor; GFR = glomerular filtration rate; PRA = plasma renin activity.

multiple indicator technique,⁸ or increased, using radionuclide angiography.⁹ In relation to this, atrial volumes appear to be enlarged on 2-D echocardiograms, together with elevation of plasma levels of atrial natriuretic peptide (ANP).¹⁰ The elevated plasma levels of ANP appear to be a factor in compensating for the tendency toward renal sodium retention in pre-ascites.

Thus, in pre-ascitic cirrhosis, the compensated renal sodium retention appears to lead to blood volume expansion. Although requiring further elucidation, there is now evidence that one factor involved in the tendency to renal sodium retention in pre-ascites is increased renal accumulation of angiotensin II, since it can be reversed by low doses of the angiotensin II receptor antagonist, losartan.¹¹ Low dose losartan can also prevent the changes in renal sodium-handling associated with postural change in pre-ascitics.¹² The essential abnormality in these events appears to be the development of significant sinusoidal or post-sinusoidal portal hypertension (portal pressure >10 mmHg), since neither cirrhotic patients with portal pressures of less than 10 mmHg,¹³ nor patients with pre-sinusoidal portal hypertension, such as portal vein thrombosis, develop significant ascites, despite the presence of vasodilatation and hyperkinetic circulation. Other abnormalities described in pre-ascites, such as increased nitric oxide levels¹⁴ and sympathetic nerve activity,⁷ have as yet no proven association with sodium retention.

In summary, the suggestion is that at some time during the natural history of cirrhosis, but certainly some time after portal pressure has risen to over 10 mmHg, renal sodium

retention begins when the patient is in the upright position. As with the angiotensin II activation of hepatic stellate cells, this sodium retention may be due in part to localised renal accumulation of angiotensin II, resulting in compensatory blood volume expansion, and elevation of GFR, hyperkinetic circulation, suppression of PRA, and natriuresis when supine. However, the natural progression of cirrhotic patients through such stages to early decompensation and ascites has not yet been documented (Fig 2).

Early ascites (Fig 1b)

When ascites first appeared, how did the compensatory mechanisms break down leading to increased sodium retention? The answer appears to be a combination of the following: a further increase in post-sinusoidal portal hypertension;¹⁵ consequently increased splanchnic vasodilatation, associated with increased nitric oxide production; decreasing effective arterial blood volume, or CBV,⁸ and a decreasing GFR; a further increase in SNA;¹⁶ and elevation of RAAS in the majority of patients, though not all. These circulatory changes are associated, within the renal tubule, with increased proximal but predominantly distal tubule sodium reabsorption.¹⁷ The increasing proximal reabsorption of sodium results in the development of resistance to the increasing plasma levels of ANP, acting predominantly via the distal tubular receptors.¹⁰ Not surprisingly, therefore, distal diuretics, particularly spironolactone 100–200 mg as a single dose, together with a salt-restricted diet, are most effective.¹⁸ However, in some patients these pathophysiological factors continue to increase, resulting in increasing reabsorption of sodium proximal to the distal tubule. In such patients, a loop diuretic, such as furosemide, should be added in divided and stepwise increasing doses, to maximal single doses of spironolactone of 400 mg daily, to achieve successful natriuresis.¹⁸

Refractory ascites (Fig 1c)

In some patients with ascites, proximal reabsorption of sodium increases to the point where the combination of maximal divided doses of furosemide, 120–160 mg, and spironolactone,

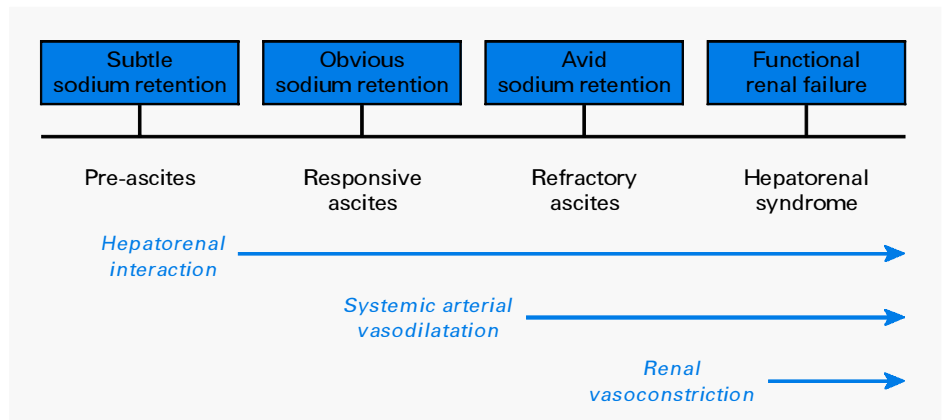


Fig 2. Stages of renal sodium retention.

400 mg, fail to achieve a natriuresis. These changes once again result from a combination of increasing portal pressure and deteriorating liver function, further vasodilatation, an increase in circulating vasoconstrictors, and a decrease in renal blood flow and GFR. This is known as refractory ascites,¹⁹ and its onset marks a sentinel deterioration in the patient's prognosis to a 50% mortality rate at two years. Therefore *all* such patients should be considered at this stage for referral for consideration for liver transplantation. The only effective medical way of decreasing proximal tubular water and sodium reabsorption in cirrhotics is with the osmotic diuretic, mannitol.²⁰ However, this has to be given intravenously and is therefore not clinically useful for chronic therapy.

Paracentesis

In patients with refractory ascites, repeated large volume or total volume abdominal paracentesis can be used, together with plasma volume expanders.²¹ With removal of 4 or less litres of ascites, we have found that replacement with intravenous albumin is not necessary.²² However, with 5 or more litres of ascites removed, we recommend replacement with 5 g of albumin per litre of ascitic fluid removed. Failure to replace losses, with a volume expander, will lead to the development of post-paracentesis circulatory syndrome in some patients.²³ This is heralded by a post-paracentesis rise in PRA, which is followed by an insidious rise in serum creatinine over a period of months, and the onset of HRS type II (see below).¹⁹ The pathophysiology of this is not completely understood, but it is clear that paracentesis results in peripheral vasodilatation that enhances effective arterial underfilling, and therefore requires acute volume expansion. Otherwise, abdominal paracentesis is a benign, ambulatory procedure resulting in less hospitalisation and side effects than maximal doses of diuretics.²¹

Transjugular intrahepatic hepatoportal shunt (TIPS)

The main disadvantages of paracentesis are, first, that it has to be repeated regularly, often with decreasing intervals of time and, second, that it does not significantly improve the overall poor prognosis of refractory ascites, compared to diuretic therapy.²¹ An alternative angiographic therapy is TIPS. Although originally designed to lower portal pressure to treat patients with refractory bleeding and oesophageal bleeding, the acute shunting of splanchnic blood back into the systemic circulation by TIPS has been shown to result in volume repletion, a fall in PRA and serum aldosterone levels, and a gradual rise in urine sodium excretion, followed by improvement in GFR and renal blood flow.²⁴ In the long term, a successfully functioning TIPS will obviate the use of diuretics,²⁵ will result in an improvement in overall nutrition and, in about half the patients, will eliminate the need for liver transplantation. However, these procedures should only be performed at specialist centres, since experience is essential for assessing such patients for the procedure, monitoring them for complications such as a blocked or poorly functioning shunt, and restoring the function of the shunt

radiologically. Recent randomised controlled trials have confirmed the survival benefits of TIPS versus paracenteses in the overall management of patients with refractory ascites.²⁶

Hepatorenal syndrome (Fig 1d, Table 2)

Hepatorenal syndrome has been divided into two types by the International Ascites Club.¹⁹ HRS type I is frequently precipitated by a number of complications in decompensated cirrhotic patients with poor liver function and ascites. In a recent large series of HRS type I patients, about 50% of the patients were undergoing paracenteses, and 50% were on diuretics.²⁷ In contrast, the majority of patients with HRS type II have a longer, more insidious onset of renal failure over several months. Until recently, HRS type I carried a mortality rate of over 80%, with a median survival of less than two weeks,¹⁹ and the only therapy for HRS was liver transplantation. This had to be performed urgently, resulting in survival rates post-transplant of around 50% – significantly poorer than those in other patient groups.²⁸ Indeed, elevated pre-transplant serum creatinine levels are clearly a poor prognostic factor post-transplant,²⁹ so much so that some authorities have suggested that the appropriate treatment for patients with hepatorenal disorders is a liver–kidney transplant.³⁰ Despite the fact that survival figures from such an approach appear to be better, it has not yet achieved the status of common practice.

Recently, however, there have been reports of improvement of

Table 2. Description of types I and II

	Type I	Type II
Mode of onset	Precipitous (days)	Gradual (months) cirrhosis
Clinical background	Cirrhosis + ineffective arterial blood volume + precipitating factors	Cirrhosis + Refractory ascites
Precipitating factors	Sepsis Upper GI bleeding Cholestatic jaundice	Aggressive diuresis Large volume paracentesis with inadequate volume replacement
Clinical course	Rapid generalised deterioration Death within 1–4 weeks	Gradual deterioration in renal function
Management (i) general	Intensive care monitoring Treat precipitating cause	Stop diuretics and/or Paracentesis
(ii) specific	Terlipressin + albumin MARS (if available) Consider urgent liver transplantation or TIPS	Terlipressin or midodrine + octreotide + albumin Consider elective TIPS or liver transplantation

GI = gastrointestinal; MARS = molecular adsorbent recirculating system; TIPS = transjugular intrahepatic hepatoportal shunt

renal function and the reversal of HRS in cirrhotic patients, using infusions of vasopressin analogues, especially terlipressin,²⁷ combined with albumin, over several days. In most cases, the response is temporary, and the treatment has acted as a 'bridge' allowing patients to undergo an elective transplant with normal serum creatinine. As a result of undergoing transplantation with improved renal function, survival figures post-transplant have improved. However, in some cases patients treated with terlipressin appeared to achieve a prolonged response of many months, or even years, rendering transplantation unnecessary. In the largest series thus far, from France, terlipressin plus albumin therapy achieved an overall 19% survival rate after several months.²⁷ However, in the 60% of patients in whom renal function improved with terlipressin therapy, the survival rate was 40% at one month.

Alternatively, patients have been treated using dialysis procedures, in which albumin-bound molecules can be removed, such as the molecular adsorbent recirculating system (MARS), operating with a continuous venovenous haemofiltration.³¹ This system incorporates a dialysis module, an asymmetric polysulphone permeable membrane which is perfused to saturation with 10% human serum albumin on both the patient and dialysate sides, in a closed-loop system. This system results in the dialysis of albumin-bound toxins from plasma onto the membrane. This albumin is recycled with deligandisation of the albumin-toxin complex, while water-soluble toxins are removed by charcoal columns. In the first controlled trial, patients received on average five daily treatment sessions, each lasting 6–8 hours. MARS significantly improved renal function, resulting in a 40% survival rate at two weeks.³¹ Again, temporary reversal of renal failure has been achieved, so that MARS therapy acted as a bridge to the possibility of elective transplantation. The numbers in this trial were small – eight patients on MARS with haemofiltration – with a mean survival of 25 days compared to four days in the five control patients with haemofiltration alone. This result will therefore need confirmation before MARS can be incorporated into the routine management of HRS.

Finally, HRS patients have also been treated with TIPS, and reversal of renal failure has been reported, achieving a survival rate of 35% at two years.³² When patients were separated into type I and type II HRS, the survival at one year in type II patients (70%) was significantly greater than in type I patients (20%).³² Such long-term successes with TIPS obviated the need for the scarce resource of liver transplantation.

Conclusion

In summary, the natural history of hepatorenal disorders in the individual cirrhotic patient spans several years. In our experience, by the time the patient develops refractory ascites there are only two treatments that can reverse progression to HRS: TIPS and liver transplantation. Therefore, using the analogy of the prophylactic treatment of esophageal varices, it behoves us to identify pre-ascitic cirrhotic patients, and study the possibility of prophylactic measures to interrupt the natural progression of hepatorenal disorders in cirrhosis.

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