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Concise Review

Pathophysiology, diagnosis and treatment of ascites in cirrhosis

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Abstract

The mechanism by which ascites develops in cirrhosis is multifactorial Severe sinusoidal portal hypertension and hepatic insufficiency are the initial factors. They lead to a circulatory dysfunction characterized by arterial vasodilation, arterial hypotension, high cardiac output and hypervolemia and to renal sodium and water retention. There are evidences that arterial vasodilation in cirrhosis occurs in the splanchnic circulation and is related to an increased synthesis of local vasodilators. Vascular resistance is normal or increased in the remaining major vascular territories (kidney, muscle and skin and brain). Splanchnic arterial vasodilation not only impairs systemic hemodynamics and renal function but also alters hemodynamics in the splanchnic microcirculation. The rapid and high inflow of arterial blood into the splanchnic microcirculation is the main factor increasing hydrostatic pressure in the splanchnic capillaries leading to an excessive production of splanchnic lymph over lymphatic return. Lymph leakage from the liver and other splanchnic organs is the mechanism of fluid accumulation in the abdominal cavity. Continuous renal sodium and water retention perpetuates ascites formation. Large volume paracentesis associated with albumin infusion is the treatment of choice of tense ascites because it is very effective and rapid and is associated with fewer complications that the traditional treatment (sodium restriction and diuretics). However, diuretic should be given after paracentesis to prevent reaccumulation of ascites. In patients with moderate ascites diuretics should be preferred as initial therapy. Patients with refractory ascites could be treated by paracentesis or percutaneous transjugular portacaval shunt (TIPS). TIPS is more effective in the long term control of ascites but may impair hepatic function and induce chronic hepatic encephalopathy.

Key words: Ascitis, cirrhosis albumin, diuretic.

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Pathogenesis of ascites in cirrhosis

Renal function abnormalities

Sodium retention

The impairment in the renal ability to excrete sodium is the earliest renal dysfunction in cirrhosis. Before the development of ascites, when patients are still compensated (compensated cirrhosis is a term commonly used to define patients prior to the development of any of the major complications of the disease: i.e. ascites, hemorrhage or hepatic encephalopathy), they present subtle abnormalities in renal sodium metabolism. For example they may not escape to the sodium retaining effect of mineralcorticoids or may be unable to excrete a sodium overload. However, as the disease progresses, patients became unable to excrete their regular sodium intake and develop sodium retention. Experimental studies in rates with carbon tetrachloride-induced cirrhosis have demonstrated a closed relationship between the onset of sodium retention and of ascites. Sodium retention preceded the onset of ascites by few days indicating that it is a cause and not a consequence of the accumulation of fluid within the abdominal cavity. At the initial phases of sodium retention, the urinary sodium excretion is only moderately reduced. However, with the progression of the disease sodium retention is very intense and the urinary sodium excretion may approach to zero. In fact cirrhosis is the human condition in which sodium retention is more intense.

Sodium retention in cirrhosis is mainly due to an increased tubular sodium reabsorption, since at the initial phases of the disease it occurs in the setting of a normal glomerular filtration rate (GFR). However, in the very advanced phases of the disease, when hepatorrenal syndrome develops, a decreased filtered sodium plays also a contributory role. Numerous mechanisms are involved in the pathogenesis of sodium retention in cirrhosis with ascites. Many of these patients present an increased activity of the sympathetic nervous systems (SNS) and of the renin-angiotensin-aldosterone system (RAAS). The renal sympathetic nervous activity estimulates sodium reabsorption in the proximal tubule, loop of Henle and distal and collecting tubules. Aldosterone estimulates sodium reabsorption in the distal nefron. Therefore both systems play an important role in the pathogenesis of sodium re-

tention in cirrhosis. However, approximately one third of patients with ascites, usually those being at the early phases of ascites development, shows sodium retention in the setting of a normal activity of the SNS and RAAS. Interestingly enough these patients, as well as those with high alsosterone and norepinephrine plasma levels, also present increased circulating plasma levels of natriuretic peptides and sodium pump inhibitors. Sodium retention at the early phases of hepatic descompensation depends of factors other than the SNS and RAAS.

Water retention

The kidney is continuously generating free water in the ascending limb of the loop of Hente by a mechanism consisting in an active reabsorption of sodium chloride without a concomitant reabsorption of water. The final volume free water excretion, therefore, depends on the amount of free water reabsorbed in the more distal segments of the nephron, the convoluted distal tubule and the collecting tubule. This process is mediated by antidiuretic hormone (ADH). When ADH is completely inhibited, for example following a water load of 20 mL/kg of body weigh, the distal nephron is almost completely impermeable to water, leading to the excretion of a high urine volume (10 mL/min or more) with low urine osmolality. This urine flow rate can be ideally divided into two parts. The first (osmolar clearance) consists in the flow rate of urine water needed to dissolve the urine solute excretion isosmotically in relation to plasma. The second consists in a flow rate of urine water free of solutes (free water clearance: urine volume-osmolar clearance). In a normal person free water clearance may range from 8 to 14 mL/min.

Most patients with cirrhosis and ascites present a reduced free water clearance and in some patients the impairment in free water excretion of so intense that they are unable to increase the urine volume and decrease the urine osmolality after a water load of 20 mL/kg of body weigh. The main clinical consequence of this feature is the retention of the water ingested with the diet. This water retention contributes to the formation of ascites. On the other hand it dilutes the body fluids and produced hyponatremia and hyposmolality. Hyponatremia in cirrhosis usually develops when free water clearance is markedly reduced, below 1 mL/min.

A non-osmotic hypersecretion of ADH is the most important mechanism of the impaired free water excretion in cirrhosis. The renal synthesis of prostaglandin E2 (PGE2), which antagonises the hydrosmotic effect of ADH, is increased in patients with cirrhosis and ascites. This feature probably explains why many cirrhotic patients with ascites are able to dilute the urine after a water load despite of having high circulating plasma levels of ADH. Non-steroidal antiinflammatory drugs, therefore, may impair the renal ability to excrete free after and induce dilutional hyponatremia in these patients. In patients with hepatorenal syndrome, the pathogenesis of water retention may be even more complex. The decrease GFR may lead to a decreased delivery of sodium chloride to the ascending limb of the lopp of Henle and, therefore, to an impaired generation of free water.

Impairment of free water excretion occurs several months after the onset of sodium retention and ascites formation. Dilutional hyponatremia is, therefore, a late event in the course of decompensated cirrhosis and indicates a short probability of survival.

Hepatorenal syndrome (HRS).

Renal vasoconstriction leading to a decrease in renal perfussion and GFR is chronologically the latest renal function abnormality in cirrhosis. Serum creatinine concentration, which is the parameter used for the diagnosis of HRS, does not increase until GFR is markedly reduced (below 40 mL/min). The normal values of serum creatinine in cirrhosis is below 1.2 mg/dL. The diagnosis of HRS is made when serum cretinine concentration is over 1.5 mg/dL and there is no data suggesting other etiologies of renal failure. The majority of patients with HRS have a GFR below 20 mL/min. Two types of HRS have been identified. The most frequent is type-2 HRS which consists in a moderate non progressive renal failure. Serum creatinine in these patients remains steady during months. The main clinical problem of these patients is refractory ascites due a lack of response to diuretic therapy. Type-1 HRS consists in a rapidly progressive renal failure within days or weeks. It usually occurs in patients who already have type-2 HRS and develop a complication (i.e. a severe bacterial infection) that acts as a precipitating factor. Patients with type-2 HRS has a short probability of survival (months). The probability of survival in patients with type-1 HRS is extremely short (days or weeks).

HRS is related to a marked overactivity of the RAAS, SNS, ADH and other endogenous vasoconstrictor factors (i.e. endothelin) that overcomes the renal production of vasodilatory substances (PGE2, prostacyclin, nitric oxide, natriuretic peptides). This imbalance between vasoconstrictors and renal vasodilator mechanisms leads to renal vasoconstriction, hypoperfusion and decreased GFR. One renal hypoperfusion has developed it may further decrease the renal synthesis of vasodilators and increase the intrarenal synthesis of vasoconstrictors (angiotensin-II, adenosine, endothelin), thus leading to a vicious circle that perpetuates the renal failure.

Abnormalities in systemic hemodynamics

Arterial hypotension due to a decrease in peripheral vascular resistance, high cardiac output and hypervolemia are characteristic features in patients with descompensated cirrhosis and ascites. Arterial pressure is particularly low in patients with HRS. The stimulation of the RAAS, SNS and ADH, which are powerful vasoconstrictors, in patients with cirrhosis and ascites is a compensatory mechanism to main-

tain arterial pressure within normal or near normal limits. In fact, the administration of antagonists to the vascular effect of angiotensin-II or ADH, which does not affect arterial pressure in normal conditions, is associated to a marked decrease of arterial pressure in cirrhosis with ascites. If both substances are simultaneously blocked arterial pressure decrease to levels incompatible with life. Therefore, the stimulation of the RAAS, SNS and ADH has a beneficial effect in cirrhosis. The development of sodium retention and ascites, impaired free water excretion and HRS is the prize cirrhotic patients have to pay to maintain systemic hemodynamics.

Abnormalities in splanchnic hemodynamics

There is evidence that the arterial vasodilation in cirrhosis causing the hyperdynamic circulation in cirrhosis occurs in the splanchnic circulation and is secondary to portal hypertension. In the remaining major vascular territories (kidney, brain and muscle and skin) there is an increased in vascular resistances, which correlates directly with the activity of the RAAS. The initial event of systemic circulatory dysfunction in cirrhosis is, therefore, a splanchnic arterial vasodilation. The compensatory activation of the endogenous vasoconstrictor systems causes vasoconstriction in the remaining vascular territories to maintain arterial pressure. The splanchnic arterial vascular compartment in cirrhosis shows a decreased response to the effect of catecholamines and other endogenous vasoconstrictors. This explains why the activations of the RAAS, SNS and ADH does not normalizes circulatory function in decompensated cirrhosis.

The mechanism by which portal hypertension is associated to splanchnic arterial vasodilation and resistance of the splanchnic arterioles to vasoconstrictors is not completely understood. Early studies suggested that it may be related to increased levels of circulating vasodilators (i.e. glucagon). However, at present most investigators agree that local vasodilators synthetized or released in excess in the splanchnic vascular compartment (i.e. nitric oxide, calcitonin gene related peptide, substance P) are the predominant factors. The explanation of the increased activity of these local vasodilators associated with portal hypertension is unknown. It has been hypothetized that bacterial translocation into the interstitial space in the splanchnic organs may be involved. However, since nitric oxide, substance P and calcitonin gene related peptide are neurotransmitters of the non adrenergic non cholinergic nervous systems, a nervous mechanism is another possibility.

The degree of portal hypertension in cirrhosis correlates closely with the activity of the RAAS and SNS in patients with decompensated cirrhosis. Patients with higher wedged hepatic venous pressure or wedged to free hepatic venous pressure gradient are those with higher plasma levels of renin and norepinephrine. In fact, ascites does nor develop in patients with cirrhosis if the free to wedged hepatic venous pressure gradients is below 12 mmHg. This has been interpreted as an indication that the initial event in the activation of these systems in cirrhosis is a severe sinusoidal portal hypertension, probably as a consequence of the reduction in splanchnic vascular resistance induced by the increased portal pressure. Nevertheless another possibility is that angiotensin-II, antidiuretic hormone and catecholamines, by acting on the intrahepatic vasculature and stellate cells, may increase the intrahepatic vascular resistance and portal pressure.

In addition to a decrease in splanchnic arterial vascular resistance, portal hypertension is associated to a marked increase in the escape of the intravascular fluid to the interstitial espace. Studies evaluating the escape of radiollabeled albumin from the intravascular to the extravascular compartment and to the intraperitoneal space (which estimates the fluid dynamics through the capillary wall and peritoneum and liver surface, respectively) indicate that the lympathic system is extremely efficient in returning most of the excressive hepatic and splanchnic lymph to the general circulation in cirrhosis with ascites. The transvascular escape rate of radiolabeled albumin in these patients is remarkably high (8.5% of the total intravascular mass of albumin per hour). The fraction of the transvascular escape of albumin passing into the peritoneal cavity is, however, very low (0.21%. Ascites formation is therefore the consequence of a small spill-over of the increased rate of formation of hepatic and splanchnic lymph, most of which is returned directly to the circulation through the lymphatic system. This data are consistent with the old observation that and increased flow of thoracic flow lymph (usually 8-9 L/day) is a characteristic finding in cirrhosis with portal hypertension, whether or not ascites is present. In normal subjects this flow is below one litter per day. Due to the capillarization of the hepatic sinusoids (dissapearance of the characteristic fenestra and acquisition of a basement membrane) and to the low permeability of splanchnic capillaries to proteins the ascitic fluid of cirrhotic patients characteristically present low concentration of proteins and albumin.

Pathogenesis of ascites: the forward theory.

The evolution of our concepts on the formation of ascites in cirrhosis is imitating that on congestive heart failure 25 years ago. The formation of edema in heart failure was initially considered as secondary to the increase in venous pressure due to the reduced cardiac function. The disruption of the Satarlin equilibrium in the microcirculation due to the backward increase in capillary hydrostatic pressure would lead to the accumulation of fluid in the interstitial space and the formation of pulmonary and peripheral edema (backward theory). With the demonstration of the importance of the reinin-aldosterone and sympathetic nervous systems, ADH, and renal sodium and water retention in the pathogenesis of congestive heart

failure, however, the concept on the mechanism of cardiac edema moved from the venous to the arterial vascular compartment. According to this new concept, the predominant mechanism of edema in congestive heart failure is an impairment in effective arterial blood volume secondary to the decrease in cardiac output. The high pressure baroreceptors located in the aorta, carotid sinus, and juxtaglomerular apparatus would sense the underfilling of the arterial vascular compartment, stimulating the SNS, RAAS and ADH, and inducing an increased renal tubular reabsorption of sodium and water. The retained fluid would extravasate with increased venous pressure. Additionally, the increased activity of these endogenous vasoconstrictor systems would produce systemic vasoconstriction and further decrease in the cardiac output, thus closing a vicious circle. This "forward" theory of edema formation has been important in improving the management of this condition. The administration of vasodilators decreases cardiac afterload, increases cardiac output, deactivates the vasoconstrictor systems, inproves renal function and increases the response to diuretics.

The traditional concept of ascites formation in cirrhosis also considers hepatic edema to be a direct consequence of the "backward" increase in hydrostatic pressure in the hepatic sinusoids and splanchnic capillaries due to the sinusoidal portal hypertension. This feature, together with the hypoalbuminemia, would alter the Starling equilibrium within the hepatic and splanchnic microcirculation, leading to the accumulation of fluid in the interstitial space of these vascular territories. Leakage of fluid from the interstitial space to the peritoneal cavity would occur when the formation of interstitial edema overcomes the capacity of the abdominal lymphatic system to return the hepatic and splachnic lymph to the systemic circulation. Renal dysfunction in cirrhosis would be a consequence of a reduction in the circulating blood volume secondary to the formation of ascites.

The demonstration that plasma volume and cardiac output are markedly increased in cirrhosis, and that peripheral vascular resistance is reduced, are strong arguments against this "backward" hypothesis of ascites formation.

The mechanism of ascites formation could be better explained on the basis of the changes in the arterial circulation induced by portal hypertension. The hypothesis ("forward " theory of ascites formation) considers that that the accumulation of fluid within the abdomen is a consequence of the splanchnic arterial vasodilation, which would simultaneously produce arterial vascular underfilling and a "forward" increase in the splanchnic capillary pressure and filtration coefficient. In patients with compensated cirrhosis, the degree of portal hypertension and of splanchnic arterial vasodilation is moderate. Their arterial vascular underfilling can be compensated by an increased in plasma volume and cardiac index. On the other hand, the lymphatic system is able to return to moderate increase in lymph produced to the systemic circulation, thus preventing the leakage of fluid into the abdominal cavity. As cirrhosis progresses, however, portal hypertension and the secondary fall in splanchnic vascular resistance are progressively more intense, and a critical point is reached at which the consequences of splanchnic arteriolar vasodilation can not longer be compensated for by increasing lymp return, plasma volume and cardiac index. The maintenance of arterial pressure then requires persistent activation of the RAAS, the SNS and ADH, which produces continuous sodium and water retention. The retained fluid is, however, ineffective in refilling the dilated arterial vascular bed because it escapes from the intravascular compartment, due to an imbalance between the excessive lymph production and the ability of the lymphatic system to return it to the systemic circulation. The consequence of both disorders is continuous leakage of fluid into the abdominal cavity and the formation of ascites.

Assessment of the cirrhotic patients with ascites

Diagnostic paracentesis

It is an essential procedure in the diagnostic assessment of patients with cirrhosis and ascites since they may present an ascites unrelated with the hepatic disease (i.e. tuberculous ascites in alcoholic cirrhosis or malignant ascites) or complications that require the analysis of the ascitic fluid for diagnosis (i.e. spontaneous bacterial peritonitis or hemoperitoneum secondary to the rupture of a superficial hepatocelular carcinoma).

The ascitic fluid in cirrhotics is transparent and yellow-amber in colour. Traditionally ascites in these patients is considered to have the characteristics of a transudate, with a total protein concentration of less than 2.5 g/dL and with relatively few cells. However, studies in large series of patients show that ascites protein concentration may range between 0.5 and more than 6 g/dL and is greater than 3 g/dL in up to 30 per cent of patients with otherwise uncomplicated cirrhosis. The total protein concentration in ascitic fluid correlates inversely with the portal pressure, patients with higher portal hypertension having low ascitic protein concentration. The total ascitic fluid protein concentration is also an important predictive factor for the development of spontaneous bacterial peritonitis (SBP), which usually develops in patients with an ascitic fluid protein concentration lower than 1 g/dL. The determination of the serum-ascites albumin gradient is of value in the differential diagnosis of the etiology of ascites. Patients with gradients > 1.1 g/dL usually have an ascites associated with portal hypertension.

The ascitic fluid in the cirrhotic without spontaneous bacterial peritonitis usually have fewer than 300 to 500 white blood cells per mm^3: more than 70 per cent of these cells are mononuclear leukocytes. In contrast in cirrhotic patients with SBP the ascitic fluid usually contains more

than 500 white blood cells per mm^3 (frequently more than 2,000), with more than 70% of them being polymorphonuclear leukocytes.

The concentration of red blood cells in cirrhotic ascites is usually lower than 1,000 cells per mm^3, although higher concentrations may occasionally be detected. In fact, bloody ascitic fluid, which indicates more than 50,000 red cells per mm^3 (hematrocrit of about 0.5%), occurs in approximately 2 per cent of uncomplicated cirrhotic patients with ascites.

Parameters with prognostic factors in cirrhotic patients with ascites

Of the numerous clinical and laboratory data that should be obtained during the assessment of cirrhotic patients with ascites, the following are important because they of prognostic values: mean arterial pressure, serum creatinine concentration, serum sodium concentration, urine sodium excretion, nutritional status, liver size and the standard liver function tests. It is important to remark that parameters stimating the degree of impairment of circulatory function are better predictors of survival than those estimating hepatic function. Patients with hepatorenal failure (serum creatinine > 1.5 mg/dL) have a very poor prognosis. In patients with non-azotemic cirrhosis with ascites mean arterial pressure and urinary sodium excretion are excellent prognostic factors. Patients with a mean arterial pressure [1/3 (systolic blood pressure - dyastolic blood pressure)] lower than 82 mmHg or with an urinary sodium excretion (in the absence of diuretic treatment during at least 4 days) lower than 5 mEq/L has a 50% probability of survival below 2 years. Patients with impaired renal ability to excrete free water as manifested by dilutional hyponatremia (serum sodium concentration < 130 mEq/l) have also a poor prognosis. Parameters such as plasma renin activity and plasma norepinephrine concentration, that estimate the degree of activation of the RAAS and SNS, respectively, are also very sensitive in predicting prognosis, although they are not routinely determined in the evaluation of patients with cirrhosis and ascites. A poor nutritional status and a small liver (as assessed by ecography) are also associated to a poor survival. Of the liver function tests, serum albumin concentration is the most powerful prognostic factor. Most cirrhotic patients with ascites are Child-Pugh B or C. All the above mentioned parameters are of prognostic value independently of the Child-Pugh score.

Management of patients with cirrhosis and ascites

Patients with moderate ascites

They have less than 5 litters of ascitic fluid and should be treated by moderate sodium restriction (50-90 mEq/day) and diuretics. It is well established that the basic diuretic in cirrhotic patients with ascites is spironolatone. It is more effective than furosemide, which should be considered as a complementary diuretic.

Two different schedules of diuretic treatment are used in cirrhotic patients with ascites. The most conservative schedule stars with spironolactone 100/mg day. If there is no response the dose is increased progressively to 200 mg/day and 400 mg/day. Furosemide is added at increasing doses (40, 80, and 160 mg/day) in patients not responding to 400 mg/day of spironolactone. The second strategy consists in the simultaneous administration of spironolactone and furosemide starting with 100 mg/day and 40 mg/day, respectively. If there is no response the dosages are increased to 200 mg/day and 80 mg/day and to 400 mg/day o 160 mg/day, respectively. There is a general agreement that these are the highest doses of diuretic to be used in cirrhotics. Higher doses will not increase the rate of response. The goal of diuretic treatment is to achive a loss of body weigh between 300 to 500 mg/day in patients without peripheral edema. Greater weight losses may be safe in patients with concomitant peripheral edema but may be associated with complications in patients without edema.

The most serious complication of diuretic treatment in patients with cirrhosis is hepatic encephalopathy. The mechanism is unknown. Other complications include renal failure (ascitic fluid reabsorption is a rate limited process and a contraction of circulating blood volume and renal failure may occur if the diuretic effect is greater than the reabsorption of ascitic fluid), dilutional hyponatremia (due to impairment in free water excretion secondary to hypovolemia or to the inhibition of sodium reabsorption in the loop of Henle in patients treated by furosemide), hyperkalemia and metabolic acidosis in cases treated by high doses of spironolactone, and muscle cramps. There are evidences that muscle cramps are related with the decrease in the effective blood volume rather than to changes in the electrolyte composition of the body fluids.

Patients with moderate ascites usually respond to low doses of diuretics and rarely develop complications. Once ascites has been mobilized diuretic dosages should be reduced to keep the patients without ascites.

Patients with tense ascites

They should be treated by total paracentesis (complete removal of ascites with one tap) associated with i.v. albumin infusion (8 g per litter of ascitic fluid removed). This procedure should be performed under strict sterile conditions, using specially designed needles (commercially available) with blunted edged cannulas and side holes and with the aid of a suction pump. With this technique the duration of the treatment ranges between 20 to 90 min depending on the amount of ascitic fluid and the rate of local complications are considerably reduced. Albumin is in-

fused immediately after paracentesis in 4-6 hours. The patients may be discharged from hospital within the same day or the day after the procedure.

There are numerous trials showing than paracentesis is a rapid, effective and safe therapy of ascites providing plasma volume is expanded with albumin. In fact, in several randomized controlled trials in patient with tense ascites, the incidence of hepatic encephalopathy, renal impairment and dylutional hyponatremia was remarkably lower in patients treated by paracentesis than in those treated by diuretics. If paracentesis is performed without volume expansion, most patients develop a circulatory dysfunction that, although asymptomatic, is associated to an impaired diuretic response, earlier readmission for ascites and shorter survival. Synthetic plasma expanders (dextran 40, dextran 70, polygeline) are lees effective than albumin in preventing circulatory disjunction when the amount of ascitic fluid removed by paracentesis is higher than 5 litters. The mechanism of paracentesis-induced circulatory dysfunction is an accentuation of the arterial vasodilation already present in these patients. However, the reason of this remains unknown. Following the mobilization of ascites by paracentesis, patients should be treated with diuretics to prevent the reaccumulation of ascites.

Patients with refractory ascites

Refractory ascites has recently been defined by the International Ascites Club as the ascites that can not be mobilized or the early recurrence of which (i.e., after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. Two different types of refractory ascites can be identified: 1) Diuretic resistant ascites is that which cannot mobilized or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction and maximal diuretic dosage; 2) Diuretic intractable ascites is that which cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage. Most cirrhotics with diuretic-resistant ascites have type-2 HRS, or lesser, although significant degrees of impairment in renal perfusion and GFR (increased serum creatinine to between 1.2 and 1.5 mg/dL).

The mechanism where by ascites is resistant to diuretic therapy in cirrhotics with renal failure is probably related to alterations in both the pharmacokinetics and pharmacodynamics. The access of diuretics to their sites of action, which is mainly determined by the amount of blood flowing throughout the kidneys, may be impaired in cirrhotics with renal failure due to the low renal perfusion. Moreover, the delivery of sodium chloride to the loop of Henle and distal nephron, the sites where furosemide and spironolactone inhibit sodium reabsorption, may be markedly reduced in cirrhotics with renal failure secondary to a low GFR and enhanced sodium reabsorption in the proximal tubule.

Three treatments can be used in patients with refractory ascites. LeVeen shunt, a prosthesis that communicates the peritoneal cavity with the systemic circulation, was the first treatment specifically designed for these patients. It consists in a multiperforated intraabdominal tube connected to a one-way valve and a second tube that subcutaneously reach the superior vena cava through the internal jugular vein. LeVeen shunt produces a sustained intravascular volume expansion, suppress the endogenous antinatriuretic systems and increase the renal response to diuretics. However it is associated with a high rate of shunt obstruction, which may occur in the valve or in the intravenous segment of the prosthesis and requires frequent reoperations. The one year probability of shunt obstruction has been estimated as 60%. Two other severe complications, superior vena cava thrombosis and plastic peritonitis, are also relatively frequent and may cause a superior vena cava syndrome of extremely poor prognosis and intestinal obstruction, respectively.

Therapeutic paracentesis is the second treatment proposed for patients with refractory ascites. Because these patients do not respond to diuretics they reaccumulate ascites very rapidly, so requiring frequent hospitalization for further paracentesis. However, because this treatment can be done in an outpatient regime and is very well tolerated, it is the commonest treatment used for refractory ascites. There are two randomized trials showing that the total time spent in hospital and the probability of survival is similar when comparing patients treated by paracentesis with patients treated by LeVeen shunt.

TIPS is also an effective treatment of refractory ascites. Following the relief of portal hypertension by TIPS many patients remain without ascites with minimal diuretic dosage. TIPS however may be associated to early mortality due to a deterioration of hepatic function and to a relatively high incidence of severe hepatic encephalopathy. Shunt dysfunction is another important problem. Its frequency may be as high as shunt obstruction in patients treated by LeVeen shunt. Two studies have so far been reported comparing TIPS *vs* therapeutic paracentesis in patients with refractory ascites and they disclosed different results. Lebrec et al. showed that TIPS significantly shortens the probability of survival in patients with refractory ascites. In contrast Rössle et al. showed an increased survival in patients treated by TIPS. Clearly more studies are needed on this subject.

Therefore, at present paracentesis should be considered the treatment of choice for the treatment of patients with refractory ascites. TIPS may be an alternative treatment in those patients who do not tolerate frequent paracentesis and present a relatively preserved hepatic function. At present, very few centers are using LeVeen shunt for the treatment of refractory ascitis due to the high incidence of shunt obstruction and other complications.

Treatment of patients with ascites and hepatorenal syndrome

The prognosis of patients with severe hepatorenal syndrome (patients with type-1 HRS and patients with type-2 HRS and a serum creatinine over 2 mg/dL) is extremely short (90% mortality rate within three months following diagnosis of HRS). Recent data indicate that long-term (1-2 weeks) treatment with the combination of plasma volume expansion with albumin and vasoconstrictor agents (ornipressin or terlipressin) normalizes circulatory function, the activity of the renin-angiotensin and sympathetic nervous system, serum creatinine and serum sodium concentration in patients with type 1 HRS and severe type 2 HRS. Interestingly enough, HRS did not recur following discontinuation of treatment and some patients showed a survival long enough to reach liver transplantation. Ornipressin administration is associated to a high rate of ischemic side effects. However, terlipressin given every 4 h as an i.v. bolus is as effective as ornipressin but lacks significant adverse effects. SBP is the commonest cause of type-1 HRS. Recent data indicates that plasma volume expansion at infection diagnosis is highly effective in preventing circulatory dysfunction and HRS in these patients. Therefore, at present we dispose of effective and safe prophylactive and therapeutic measures for the management of patients with severe HRS.

Management of dilutional hyponatremia

Hyponatremia in cirrhosis with ascites is asymptomatic in most patients and, because there is no commercially available drugs to improve free water excretion by the kidneys, it is usually not treated. Only in those very few patients with severe symptomatic hyponatremia (below 110 mEq/day), it is justified to give i.v. sodium chloride solutions to increase serum sodium concentration. This, however, is invariably followed by an increase in the rate of ascitic fluid formation. Water restriction is uneffective in the treatment of hyponatremia.

Water retention and dilutional hyponatremia, however, is an important event in cirrhotic patients with ascites. First, it indicates a severe impairment in liver, circulatory and renal function and, therefore, is associated with a short probability of survival. On the other hand, the impairment in free water excretion contributes to the accumulation of fluid and to the formation of ascites and edema.

During the last 10 years, effective drugs that increase free water excretion in patients with edema and dilutional hyponatremia have been synthetised. However, unfortunately, the pharmaceutical companies have so far not considered these agents important enough as to invest in their development. The kappa opioid agonist niravoline has been shown to increase free water excretion in both experimental rats with carbon tetrachloride-induced cirrhosis, ascites and dilutional hyponatremia and in human cirrhosis with ascites. This effect is mainly related to an inhibition of the release of ADH by the neurohypophysis. However, niravoline has other interesting effects. For example it increases free water excretion in isolated perfused kidneys, indicating the existence of a local intrarenal mechanism of action. In addition it improves systemic hemodynamics and suppress plasma renin activity indicating a beneficial circulatory effect. No data exist concerning the potential effect of niravoline to induce hepatic encephalopathy.

The physiological effect of ADH depends on its interaction with two different types of receptors. Interaction of ADH with the V1 receptors, which are the vascular receptors, leads to vasoconstriction. Interaction of ADH with the V2 receptors, which are mainly located in the collecting tubules, leads to renal water retention. At present several non-peptide V2 receptor antagonists have been develop. They are very potent in increasing free water excretion in both experimental cirrhotic rats with ascites and dilutional hyponatremia and in patients with cirrhosis and ascites.

It is, therefore, very likely that in a very near future patients with cirrhosis and ascites will be treated with diuretics and if they are hyponatremic, with acuretic drugs.

Liver transplantation

The overall 1 year survival following liver transplantation in cirrhotic patients with ascites is 85%. This figure is higher than that occuring spontaneously. Therefore, any patient with cirrhosis who develops ascites should be considered as a potential candidate for liver transplantation. The policy for deciding the point a which a patient should be listed for liver transplantation largely depends on local factors such as organ availability and waiting time. When the duration of the waiting list is prolonged (> 1 year) ascites in itself should be considered as an indication for listing for liver transplantation. When the waiting list is below 1 year then other prognostic factors such as refractory ascites, previous SBP, urinary sodium excretion lower than 10 mEq/day, dilutional hyponatremia, persistent arterial hypotension (mean arterial pressure lower than 80 mmHg) or HRS may be considered.

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