Special Article

Definition and Diagnostic Criteria of Refractory Ascites and Hepatorenal Syndrome in Cirrhosis

VICENTE ARROYO,[1] PERE GINÈS,[1] ALEXANDER L. GERBES,[2] FRANCIS J. DUDLEY,[3] PAOLO GENTILINI,[4] GIACOMO LAFFI,[4] TELFER B. REYNOLDS,[5] HELMER RING-LARSEN,[6] AND JÜRGEN SCHÖLMERICH[7]

During the last decade great advances have been made concerning the pathogenesis and treatment of ascites. A new hypothesis on the mechanism of renal dysfunction and ascites formation in cirrhosis has been proposed[1] and this has greatly stimulated research in this area. The discovery of the important role played by the vascular endothelium in the homeostasis of systemic hemodynamics and renal function[2,3] has also opened an important field of research into pathophysiology, and evidence has been presented implicating endothelial factors in the pathogenesis of systemic circulatory dysfunction in cirrhosis[4,5] and hepatorenal syndrome (HRS).[6] The reintroduction of therapeutic paracentesis has greatly modified the treatment of cirrhotic patients with tense or refractory ascites.[7] The transjugular intrahepatic portosystemic shunt is another therapeutic tool of potential interest in the management of refractory ascites.[8] The synthesis of orally-active specific antagonists of the tubular effect of antidiuretic hormone and inhibitors of antidiuretic hormone release will probably add new drugs to the pharmacological armamentarium for patients with cirrhosis and ascites. These "aquaretic drugs," which normalize renal water metabolism in experimental cirrhosis and ascites,[9-11] are of potential interest for the treatment of water retention and dilutional hyponatremia in human cirrhosis. Finally, the field of spontaneous infection of ascitic fluid (spontaneous bacterial peritonitis) is also experiencing major changes. The demonstration of intestinal bacterial translocation in experimental models of cirrhosis,[12] the potential role of cytokines in some complications associated with this infection,[13] the identification of subgroups of cirrhotic patients predisposed to develop spontaneous bacterial peritonitis,[14] and the effectiveness of selective intestinal decontamination in the primary and secondary prophylaxis of spontaneous bacterial peritonitis[15,16] are the most relevant developments.

In clear contrast to these advances, little attention has been paid to the standardization of the nomenclature and diagnostic criteria of different syndromes associated with ascites in cirrhosis. The existence of a uniform language, however, is essential in modern medicine. It facilitates communication among clinicians and researchers and ensures unambiguous diagnoses and more confident prognoses. Moreover, it improves pathophysiological and therapeutic investigations, simplifies the analysis of therapeutic trials, and stimulates multicenter studies.

PREVIOUS CONSENSUS DEFINITIONS OF HEPATORENAL SYNDROME AND REFRACTORY ASCITES

On only two occasions were syndromes associated with ascites in cirrhosis defined by a consensus approach. In 1978 a consensus conference was organized in Sassari, Italy, to define and propose diagnostic criteria for the HRS.[17] The proposals of this conference are depicted in Table 1. Ten years later, a working team organized during the Thirteenth International Congress of Gastroenterology in Rome, Italy, defined refractory ascites in cirrhosis as ascites that cannot be mobilized despite imposition of dietary sodium restriction (40 mEq/d) together with high dose diuretic therapy (400 mg/d of spironolactone plus 160 mg/d of furosemide).[18] The proposals made in Sassari, Italy, need to be modified in the light of new developments in the field of HRS research, and the definition of refractory ascites agreed upon in Rome, Italy, may be too strict as indicated by the responses of most of the 295 practicing gastroenterologists and hepatologists answering a questionnaire during the Meeting of the European As-

Abbreviations: HRS, hepatorenal syndrome; IAC, International Ascites Club; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; NE, norepinephrine; ADH, antidiuretic hormone; NSAIDs, nonsteroidal anti-inflammatory drugs; BUN, blood urine nitrogen; ATN, acute tubular necrosis.

From the [1]Liver Unit and Department of Medicine, Hospital Clínic i Provincial of Barcelona, Barcelona, Catalunya, Spain; [2]Department of Medicine II, Klinikum Grosshadern, University of Munich, Munich, Germany; [3]Department of Gastroenterology, Alfred Hospital, Victoria, Australia; [4]Clinica Medica II, University of Florence School of Medicine, Florence, Italy; [5]Liver Service, Rancho Los Amigos Hospital, University of Southern California, Downey, CA; [6]Division of Hepatology, Righshospitalet, University of Copenhagen, Copenhagen, Denmark; and [7]Department of Internal Medicine, University Hospital, Regensburg, Germany.

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Address reprint requests to: Vicente Arroyo, MD, Liver Unit, Hospital Clínic i Provincial, Villarroel 170, 08036 Barcelona, Catalunya, Spain.

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TABLE 1. The Sassari's Diagnostic Criteria of Hepatorenal Syndrome

Major criteria
Renal insufficiency (plasma creatinine >1.5 mg/dL) that progresses over days or weeks in the presence of severe liver disease and in the absence of recognized nephrotoxic agents.
Tubular function initially intact as measured by:
U/P Osm >1.0
U/P creatinine >30
UNa remarkably low: <10 mEq/L, often <5 mEq/L
The above findings undergo no sustained improvement with expansion of the intravascular space to achieve a central venous pressure up to 10 cm H_2O.
Additional Minor Criteria
The urine may or may not contain trace amounts of protein and the sediment may or may not contain hyaline and/or granular casts.
Urine volume usually small (<800 mL/d) but not invariably so.
The onset of renal failure may occur spontaneously in the course of liver disease or may be associated with infection or bleeding, paracentesis, diuretic therapy or other forms of volume loss.
The initial characteristics of the renal failure may be followed in a few to several days by tubular dysfunction characterized by isotonic urine, increased UNa, and a fall in U/P creatinine. These changes may be accompanied by an accelerated increase in plasma creatinine concentration.
Post-mortem renal histology is variable, nonspecific and may be normal.

Abbreviations: U/P, urine to plasma; UNa, urine sodium.

sociation for the Study of the Liver held in Palma de Mallorca, Spain, in 1991.[19] Moreover, the introduction of paracentesis has modified the therapeutic approach and may have changed the diagnostic criteria of refractory ascites in cirrhosis. For these reasons there seems to be a need for a redefinition of these syndromes.

IMPLEMENTATION OF CHANGES IN TERMINOLOGY AND DIAGNOSTIC CRITERIA IN MEDICINE

The process that should be followed when implementing a change in terminology or diagnostic criteria has recently been delineated.[20] Briefly, the need for such a change must be recognized by an international scientific society dedicated to the study of the subject. The society must delegate representatives with established expertise to review the old nomenclature, discard archaic concepts, and propose modifications. Their proposals should be based on appropriate justifications and submitted for review and endorsement by the sponsoring organization and by a specialized journal.

The procedure followed to elaborate the definition and diagnostic criteria of refractory ascites and HRS in cirrhosis included in this report has taken these principles into account. The International Ascites Club (IAC) is a scientific society founded in Florence, Italy, in 1990. The IAC is ruled by a committee of six members (two from Europe, two from the United States, one from Canada or Australia, and one from other areas of the world) elected every 4 years, one acting as secretary. The aim of IAC is to stimulate research on the mechanisms of circulatory and renal dysfunction in liver diseases and on the pathogenesis and treatment of ascites, HRS, and spontaneous bacterial peritonitis. At present the IAC has 181 registered members. The IAC organizes a meeting every 2 years in connection with the meetings of the European or American Association for the Study of Liver Diseases. During the IAC Meeting in Vienna, Austria, in 1992, the scientific committee decided to organize a consensus conference in order to elaborate new definitions and diagnostic criteria of refractory ascites and HRS in cirrhosis. A panel of nominated experts presented their proposals to the members of the society during their meeting in Chicago in 1994 for discussion and agreement. The current article reports the results of this consensus conference.

TYPES OF RENAL FUNCTION ABNORMALITIES IN CIRRHOSIS AND FACTORS INVOLVED IN THEIR PATHOGENESIS

Although a detailed discussion of the pathogenesis and treatment of ascites and mechanisms of renal dysfunction in cirrhosis is beyond the scope of the current report, a brief review of these topics is pertinent for a better understanding of the proposals.

Sodium Retention. The earliest change in renal function in cirrhosis is a reduced ability to excrete sodium, that may be already present in patients with compensated cirrhosis.[21] However, this abnormality does not become clinically manifest until the capacity to excrete sodium is markedly reduced and patients are unable to eliminate their dietary sodium intake. Sodium and water then accumulate in the abdominal cavity as ascites. The degree of sodium retention in cirrhosis with ascites varies considerably from patient to patient, although in most cases sodium excretion is markedly reduced or even virtually absent. Sodium retention in many patients with cirrhosis occurs in the setting of a normal glomerular filtration rate (GFR). In other cases, however, GFR is reduced. Sodium retention in the former group is because of an excessive tubular sodium reabsorption that takes place both in the proximal tubule and the distal part of the nephron. In the second group, reduced filtered sodium may also play an important role.

The mechanism(s) of increased tubular sodium reabsorption in cirrhosis is multifactorial. The overactivity of the renin-angiotensin-aldosterone system (RAAS) probably plays an important pathogenic role in this abnormality because plasma aldosterone levels are increased in most patients with cirrhosis and ascites, and correlate inversely with sodium excretion.[22] Moreover, the administration of spironolactone, a specific aldosterone antagonist, increases sodium excretion in the great majority of patients with ascites without renal failure.[23] Another major factor in the pathogenesis of sodium retention in cirrhosis is the sympathetic ner-

vous system (SNS).[24] The plasma concentration of norepinephrine (NE) in the systemic circulation, an index of the degree of activation of SNS, is increased in most patients with ascites and normal or only slightly elevated in patients without ascites.[24] Moreover, there is an inverse correlation between plasma NE levels and sodium excretion. More direct evidence of an overactivity of SNS in cirrhosis with ascites has been obtained by studies showing an increased total spillover of tritiated NE to plasma or by directly measuring the sympathetic nerve activity from peripheral muscular nerves.[25-28] In these studies, a close relationship was also observed between SNS activity and sodium retention. Measurements of NE release and spillover in selected vascular territories, including kidneys, splanchnic organs, heart, and muscle and skin, indicate that in cirrhosis there is a generalized activation of the SNS.[29,30] Further evidence for an important role of the increased renal sympathetic nerve activity in the pathogenesis of sodium retention derives from studies in experimental animals.[31-34] Bilateral renal denervation improves sodium retention in cirrhotic rats with ascites, as indicated by an increase in sodium excretion after the administration of an acute sodium load and a reduction of the positive cumulative sodium balance in chronic metabolic studies. However, despite these important evidences indicating a role for the RAAS and SNS in the pathogenesis of sodium retention in cirrhosis, a significant proportion of cirrhotic patients with ascites and marked sodium retention has normal levels of plasma renin activity, aldosterone, and NE concentration, indicating that sodium retention can occur in the absence of activation of these two antinatriuretic systems.[35] This suggests that other factors are also involved. The recent finding of an altered relationship between renal perfussion pressure and natriuresis in cirrhotic rats with ascites and renal denervation suggests that intrarenal mechanisms may play a role in renal sodium retention in cirrhosis.[36] Finally, the circulating plasma levels of atrial and brain natriuretic peptides are increased in cirrhotic patients with ascites, indicating that sodium retention in cirrhosis is not because of a deficient synthesis and/or release of these natriuretic hormones.[37]

Water Retention. Cirrhotic patients also develop an impaired renal ability to excrete free water.[38] Chronologically, this disorder occurs after the onset of sodium retention.[39] In fact, the renal ability to excrete free water, as estimated by free water clearance after a water load, is normal in patients with compensated cirrhosis as well as in a significant proportion of patients with cirrhosis and ascites. However, in most patients with ascites free water clearance is reduced.[38] When the renal ability to excrete free water is markedly impaired patients become unable to eliminate excess ingested water and develop dilutional hyponatremia.

The pathogenesis of water retention in cirrhosis is complex and probably involves several factors, including increased plasma levels of antidiuretic hormone (ADH), reduced renal synthesis of prostaglandins, and reduced delivery of filtrate to the ascending limb of the loop of Henle, the diluting segment of the nephron.[38,40] Studies in humans and experimental animals have provided strong evidence indicating that ADH plays a major role in the pathogenesis of water retention in cirrhosis. The plasma concentration of ADH is frequently increased in cirrhotic patients and correlates closely with the reduction in solute-free water excretion; patients with higher plasma concentrations of ADH generally have the more severe impairment in water metabolism.[41-43] Longitudinal studies in rats with cirrhosis and ascites have shown the existence of a chronological relationship between ADH hypersecretion and impairment in water excretion.[39] In addition, kidneys from cirrhotic rats with ascites show increased gene expression of aquoporin, the ADH-regulated water channel.[44] Moreover, Brattleboro rats (rats with a congenital deficiency of ADH) with cirrhosis do not develop an impairment in water excretion.[45] Finally, the administration of specific antagonists of the tubular effect of ADH (V2 antagonists) restore the renal ability to excrete free water in cirrhotic rats.[9,10] The increased plasma ADH concentrations in cirrhosis are because of an increased hypothalamic synthesis and not because of a reduced systemic clearance.[46,47] This increased synthesis of ADH is related to a nonosmotic hypersecretion of the peptide, because most patients have a degree of hyponatremia and hypoosmolality that would suppress ADH release in normal subjects.[42,43] Renal prostaglandin E2 also contributes to the maintenance of water excretion in nonazotemic cirrhotic patients with ascites because the inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs (NSAIDs) in these patients is associated with an impairment of free water excretion independently of changes in renal hemodynamics.[42] Finally, there is indirect evidence that an impaired distal delivery of filtrate because of a reduced GFR and/or an enhanced proximal sodium reabsorption also plays an important role in the impaired water excretion.[38] Although conclusive data about the relative importance of these three different factors in the pathogenesis of water retention in patients with cirrhosis are lacking, it is likely that ADH and renal prostaglandins are the main pathogenic factors in patients without renal failure whereas a reduced distal delivery of filtrate plays an important role in water retention in patients with HRS.

Renal Vasoconstriction. Renal vasoconstriction leading to reduction of renal blood flow and GFR is, chronologically, the latest renal function abnormality in cirrhosis. It may range from a modest impairment of renal hemodynamics, only detectable by measuring renal plasma flow and GFR by clearance techniques, to an intense renal vasoconstriction and severe renal failure.

Renal vasoconstriction in cirrhosis occurs in the setting of a marked stimulation of several renal vasoconstrictor factors, including the RAAS and SNS, ADH and endothelin that suggests that they may participate in the pathogenesis of this abnormality.[48-50] The RAAS is markedly activated in patients with HRS, supporting

a role for angiotensin II in the pathogenesis of renal vasoconstriction. However, because the interruption of RAAS is associated with arterial hypotension in patients with high-plasma renin activity, the effects of RAAS on renal function independent of those on systemic hemodynamics have not been possible to assess. As with the RAAS, the overactivity of the SNS is particularly intense in patients with HRS and arterial and renal venous NE concentration correlate inversely with renal blood flow.[51] Moreover, anesthetic blockade of the lumbar SNS, a maneuver that reduces the activity of the kidney SNS, partially reverses renal dysfunction in patients with HRS.[52] ADH may also contribute to renal vasoconstriction because plasma ADH levels correlate inversely with renal blood flow and GFR.[42] Finally, the circulating levels of endothelin, a very potent renal vasoconstrictor agent, are also increased in patients with cirrhosis, specially in those with more intense renal vasoconstriction.[6]

An impaired synthesis of renal vasodilator substances has also been implicated in the pathogenesis of renal vasoconstriction in cirrhosis. Several studies have shown that patients with HRS have lower urinary excretion of prostaglandin (PG) E_2 and 6-keto-$PGF_{1\alpha}$ than patients with ascites without renal failure.[53-55] Moreover, patients with HRS have a reduced renal content of prostaglandin H2 synthetase (medullary cyclooxigenase).[56] Further support for this hypothesis derives from studies investigating the effect of NSAIDs in patients with cirrhosis. The administration of these drugs to patients with ascites and marked sodium retention causes a marked inhibition of renal prostaglandin synthesis associated with a profound renal vasoconstriction.[53,54,57] Because patients with HRS have the greatest activation of renal vasoconstrictor systems, an imbalance between vasoconstrictor systems and the renal production of vasodilator prostaglandins has been proposed to explain the marked reduction of renal blood flow and GFR that occurs in this condition.[58] Recent studies in experimental animals have presented evidences indicating that other vasodilator substances, including nitric oxide and natriuretic peptides, also participate in the maintenance of renal hemodynamics in cirrhosis.[59,60]

PATHOGENESIS OF ASCITES AND RENAL DYSFUNCTION IN CIRRHOSIS

General agreement exists that the initial event of renal dysfunction and ascites formation in cirrhosis is the combination of increased sinusoidal pressure and a certain degree of hepatic insufficiency. This assumption is based on studies showing higher sinusoidal pressure and more impaired liver function in cirrhotic patients with ascites as compared with those with compensated cirrhosis (patients who have never had ascites)[61] and on the fact that ascites or HRS are extremely uncommon in patients submitted to surgical portasystemic shunts.[62] However, the mechanism by which the diseased liver affects renal function is not yet fully understood.

Traditional Underfilling Hypothesis. The traditional concept considers that the link between the liver and the kidney in cirrhosis is the "backward" increase in hydrostatic pressure within the hepatic and splanchnic microcirculation secondary to the intrahepatic blockade of the hepatic blood flow, that leads to increased formation of lymph in these vascular territories. When lymph production exceeds lymphatic return, ascites develop resulting in contraction of the circulating blood volume and secondary renal dysfunction.[63]

Overflow Hypothesis. Several investigations performed during the 1960s and 1970s have shown that circulating blood volume is markedly increased in cirrhotic patients with and without ascites, and significant sodium retention precedes the development of ascites in experimental models of cirrhosis. Moreover, because ascites formation can be induced in patients with compensated cirrhosis by the administration of mineralocorticoids, an "overflow theory" of ascites was proposed.[64] According to this hypothesis, the increased sinusoidal pressure, presumably through a hepatorenal reflex,[65] induces "primary" sodium and water retention (primary in the sense that it is independent of changes in systemic hemodynamics) and secondary increase in plasma volume and cardiac index. The peripheral vascular resistance decreases to accommodate the high-circulating blood volume. The encounter between the expanded arterial blood volume and the increased hydrostatic pressure in the hepatic and splanchnic microcirculation leads to overflow ascites formation.

Peripheral Arterial Vasodilation Hypothesis. The "peripheral arterial vasodilation hypothesis"[1] was proposed in 1988 because many features of cirrhotic patients with ascites could not be satisfactorily explained on the basis of the traditional underfilling or overflow theories. Arterial hypotension is a frequent finding in patients with cirrhosis and ascites, particularly in cases with renal failure, despite an increased plasma volume and cardiac index, and a stimulated RAAS, SNS, and ADH, that are all powerful vasoconstrictors. In experimental models of cirrhosis hyperaldosteronism and sodium retention occur in close chronological relationship with a decrease in arterial pressure. The blockade of the vascular effect of angiotensin II and ADH in cirrhosis with ascites is associated with a marked fall in peripheral vascular resistance and arterial pressure, an effect not observed in normal individuals or patients with expanded circulating blood volume. Finally, portal hypertension is constantly associated with a marked splanchnic arteriolar vasodilation that may cause arterial hypotension and activation of endogenous vasoconstrictor systems.

According to this hypothesis, splanchnic arteriolar vasodilation secondary to portal hypertension is the initial event, baroreceptor-mediated activation of RAAS, SNS, and ADH because of underfilling of the arterial vascular compartment (not because the circulating blood volume is decreased but because the arterial vascular compartment is disproportionally enlarged) the intermediate step, and renal sodium and

water retention the final consequence. Splanchnic arteriolar vasodilation may play a critical role not only in altering systemic hemodynamics but also in the increased microvascular hydrostatic pressure and, therefore, in the passage of fluid from the intravascular compartment to the interstitial space during portal hypertension.[66]

TREATMENT OF ASCITES IN CIRRHOSIS

Dietary Sodium Restriction. The aim of medical treatment of ascites is the mobilization of intraabdominal fluid by creating a negative sodium balance. In patients who spontaneously eliminate relatively large amounts of sodium in the urine, who represent approximately 10% to 20% of the cases with ascites, this can be obtained simply by reducing the sodium content of the diet. However, in the remaining cases with marked sodium retention a negative sodium balance cannot be achieved unless patients receive diuretics. Although sodium restriction may not be necessary for the mobilization of ascites in patients with good response to diuretics, it is essential in cases responding poorly to these drugs. The design of a low sodium diet for a cirrhotic patient with ascites requiring prolonged sodium restriction must take into account not only the sodium content but also the palatability of the diet and its nutritional value. These different aspects are difficult to balance in diets containing less than 40 to 60 mEq/d of sodium.

Diuretics. Spironolactone and loop diuretics (furosemide, bumetanide) are the diuretics most often used for the treatment of ascites in cirrhosis.

Spironolactone is rapidly and almost completely absorbed from the gastrointestinal tract and undergoes extensive metabolism leading to numerous biologically-active compounds. They are tightly bound to plasma proteins, from which they are slowly released to the kidneys; e.g., the half-life of canrenone, one of the major metabolites of spironolactone, has been estimated to be in the range of 10 to 35 hours in healthy subjects and may be even longer in cirrhotic patients.[67,68] Spironolactone metabolites act by competitively inhibiting the binding of aldosterone to a specific receptor protein in the cytoplasm of the distal and collecting tubular cells. The action of aldosterone involves the interaction with a cytosolic receptor, followed by a secondary interaction with a receptor located in the nucleus.[69] A long-lived aldosterone-induced protein is then produced that stimulates sodium reabsorption mechanisms. These pharmacological characteristics explain the lag of 2 to 4 days from the initiation or discontinuation of spironolactone therapy to the onset or termination of the natriuretic effect.

The natriuretic activity of spironolactone and its metabolites in cirrhosis depends on their plasma concentration, degree of hyperaldosteronism, and delivery of sodium to the distal nephron.[23,70] The effective dosage of spironolactone correlates directly with plasma aldosterone concentration, patients with marked hyperaldosteronism requiring high doses of the drug (400 to 600 mg/d). Between 20% to 30% of patients with nonazotemic cirrhosis and ascites do not respond to high-spironolactone dosage (500 mg/d).[70] These cases have a poor distal delivery of filtrate.

Furosemide is highly bound to plasma proteins and reaches the tubular lumen by active secretion in the proximal tubule. Once in the luminal compartment, furosemide reaches the luminal membrane of the cells of the ascending limb of the loop of Henle, where it blocks a specific cotransport system and inhibits chloride and sodium reabsorption.[71] Furosemide has no effect on the distal nephron. The natriuretic effect of furosemide is partially mediated by prostaglandins and is decreased by NSAIDs administration.[72] Between 20% and 50% of the filtered sodium is reabsorbed in the loop of Henle. This explains the natriuretic potency of furosemide, which, at a high dosage, may increase sodium excretion by as much as 30% of the filtered sodium in normal subjects. Furosemide is rapidly absorbed from the gut and the onset of action takes place within 30 minutes following its oral administration. The natriuretic effect peaks within 1 to 2 hours and vanishes after 3 to 4 hours in normal subjects; a sigmoidal relationship exists between natriuresis and urinary furosemide excretion. Natriuretic response, therefore, is parallel to the rate of diuretic excretion.

The administration of relatively high doses of furosemide (up to 160 mg/d) to nonazotemic cirrhotics causes a satisfactory natriuresis in only 50% of patients.[23,73] Mechanisms involved in this poor diuretic effect include reduced renal clearance of furosemide, decreased delivery of fluid to the loop of Henle because of an enhanced proximal sodium reabsorption and, finally, hyperaldosteronism. The consequence of this latter mechanism is that most of the sodium not reabsorbed in the loop of Henle by the action of furosemide is subsequently taken up in the distal nephron. Thus, the association of furosemide and spironolactone increases the natriuretic effect of each drug.

Two different diuretic schedules are usually used in cirrhosis. The first consists of the administration of increasing (every 3 days) doses of spironolactone, adding furosemide only to those patients not responding to the highest recommended doses of spironolactone. The second consists of the simultaneous administration of furosemide and spironolactone from the beginning of the treatment, increasing the doses of both diuretics if no therapeutic response is achieved. There is no study comparing these two treatment schedules. Recent studies suggest that torasemide, a new loop diuretic, induces higher natriuresis and diuresis than furosemide in cirrhotic patients with ascites.[74]

Side Effects of Diuretics in Cirrhosis. The most important complication of diuretic therapy is hepatic encephalopathy, that has been estimated to occur in approximately 25% of hospitalized cirrhotic patients with tense ascites treated with diuretics.[75,76] Diuretic-induced hepatic encephalopathy has traditionally been considered secondary to hyperammonemia because of an increased renal ammonia production following di-

uretic-induced hypokalemia and alkalosis.[77] However, recent studies have shown that some diuretics may also impair the urea cycle leading to reduced hepatic transformation of ammonia to urea.[78]

Diuretic-induced renal impairment, as defined by a significant increase in blood urea nitrogen or serum creatinine concentration during an effective diuretic treatment, has been estimated to occur in approximately 20% of hospitalized cirrhotic patients with ascites[75,76] and is particularly common in patients without peripheral edema.[79] It develops when the rate of diuresis exceeds the rate of ascites reabsorption, leading to intravascular volume depletion and decrease in renal perfusion and GFR. Diuretic-induced renal impairment, therefore, occurs in patients responding to diuretic treatment with loss of body weight and significant natriuresis. Diuretic-induced renal impairment is usually moderate and rapidly reversible following diuretic withdrawal.

Hyponatremia, occasionally severe, that has been estimated to occur in approximately 30% of hospitalized cirrhotic patients with ascites treated with diuretics[75,76] is secondary to an impairment of the already decreased renal ability to excrete free water. Furosemide may directly impair free water excretion (the generation of free water within the kidney is the result of the reabsorption of sodium chloride without the concomitant reabsorption of water in the water-impermeable ascending limb of the loop of Henle). On the other hand, any type of diuretic, by producing volume depletion, may stimulate the release of ADH and decrease the delivery of filtrate to the diluting segment of the nephron.

Hypokalemia is a frequent side effect in cirrhotic patients with ascites treated with furosemide alone. It is because of hypersecretion of potassium secondary to an increased distal sodium delivery. Treatment with high doses of spironolactone may induce severe hyperkalemia, particularly in patients with renal failure, possibly by a mechanism unrelated to urinary potassium excretion.[80] The simultaneous administration of furosemide and spironolactone markedly decreases the incidence of these side effects. Severe metabolic acidosis because of impaired distal secretion of H+ ions has been reported in cirrhotic patients with ascites treated with high doses of spironolactone.[81]

Other Therapeutic Measures. During the last decade several randomized controlled trials performed in hospitalized cirrhotic patients with tense ascites have shown that therapeutic paracentesis, either as repeated large-volume paracentesis or as total paracentesis, associated with volume expansion with intravenous albumin is more effective than conventional diuretic therapy in the mobilization of ascites.[7,82,83] It is associated with a lower incidence of complications, and reduces the duration of hospitalization and the cost of treatment considerably.[82,83] Based on these studies, therapeutic paracentesis has been proposed as the treatment of choice for tense ascites in cirrhotic patients. Because therapeutic paracentesis does not improve renal function, patients treated by paracentesis require diuretic treatment to avoid reaccumulation of ascites.

Peritoneovenous shunting in cirrhotic patients with ascites induces a sustained expansion of the circulating blood volume, suppression of renin, aldosterone, NE, and ADH, improvement in renal function, and increased responsiveness to diuretics.[84] Unfortunately, this therapeutic measure is associated with a high rate of complications. Obstruction of the prosthesis, that often requires reoperation and occurs in more than 40% of cases during the first postoperative year, is the most important problem. A recent controlled trial in cirrhotic patients with refractory ascites comparing therapeutic paracentesis and LeVeen shunt has shown that although peritoneovenous shunting is better than paracentesis in the long-term control of ascites, it does not reduce the total time in hospital during follow-up or increase survival.[85]

HISTORICAL ASPECTS ON REFRACTORY ASCITES

Although the term "refractory ascites" (or "intractable ascites", "resistant ascites" or "problematic ascites") was introduced in the 1950s to define ascites not responding to sodium restriction and diuretics,[86] it was not until the next decade that it reached widespread use. The medical therapy of ascites prior to the 1960s consisted of sodium restriction and administration of mercurial diuretics or thiazides and this therapeutic schedule was effective in only a small proportion of patients. Therefore, refractory ascites was the rule and not an exception. The early 1960's represented an important period for ascites therapy development. Loop diuretics and spironolactone were introduced and represented a major therapeutic step forward. The efficacy of the combination of sodium restriction, spironolactone, and furosemide in most patients with ascites, together with the high incidence of complications of paracentesis because of an inappropriate technique, led to the abandonment of this procedure. In fact, most authors of textbooks of Hepatology published during the 1960s and the 1970s found therapeutic paracentesis contraindicated in cirrhotic patients. Refractory ascites then appeared as an important therapeutic challenge in clinical hepatology.

During the last two decades several therapeutic approaches have been tested in cirrhotic patients with refractory ascites, including surgical portacaval anastomosis,[87] paracentesis with reinfusion of unmodified or concentrated ascitic fluid into the systemic circulation,[88,89] paracentesis and reinfusion of concentrated ascitic fluid into the peritoneal cavity,[90] peritoneo-venous shunting,[91] therapeutic paracentesis associated with intravenous albumin infusion[85] and, lately, the transjugular intrahepatic portacaval shunt.[8] A critical analysis of the articles describing these procedures reveals the need for a standardized nomenclature because although some investigations only deal with patients not responding to a low-sodium diet and

diuretics, other include patients who cannot be treated with diuretics because of the development of side effects or cases that respond to diuretics but who develop frequent episodes of ascites. The degree of sodium restriction and the diuretic dosage also vary markedly from one study to another, sodium intake ranging from 20 to 100 mEq/d, spironolactone dosage from 200 to 600 mg/d, and furosemide dosage from 80 to 200 mg/d.

The incidence of ascites refractory to diuretic therapy is another aspect insufficiently investigated. In patients with nonazotemic cirrhosis with ascites an incidence of 5% to 10% has recently been reported.[92] However, the incidence of refractory ascites in patients with moderate renal failure may be considerably higher.

PROPOSED DEFINITION AND DIAGNOSTIC CRITERIA OF REFRACTORY ASCITES IN CIRRHOSIS

The definition and diagnostic criteria of refractory ascites proposed have been based on the following assumptions: (1) a general term defining ascites that cannot be satisfactorily managed by medical therapy should be available; (2) refractory ascites is not a unique condition. Each subtype of refractory ascites should have a specific name; and (3) diagnostic criteria of each one of these subtypes of refractory ascites should be clearly established.

Definitions

Refractory Ascites. Ascites that cannot be mobilized or the early recurrence of which (i.e., after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. The term "refractory ascites" includes two different subtypes: "diuretic-resistant ascites" and "diuretic-intractable ascites".

Diuretic-resistant Ascites. Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction and intensive diuretic treatment.

Diuretic-intractable Ascites. Ascites that 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.

Diagnostic Criteria

Ascites. The term ascites in all definitions refers to grade 2 or 3 clinically-detectable ascites (grade 1: mild ascites; grade 2: moderate ascites; and grade 3: massive or tense ascites).

Mobilization of Ascites. Decrease of ascites at least to grade 1.

Treatment Period to Define Refractory Ascites. Patients must be on intensive diuretic treatment, for at least one week.

Lack of Response. Mean loss of weight less than 200 g/d during the last 4 days of intensive diuretic therapy and urinary sodium excretion less than 50 mEq/d.

Dietary Sodium Restriction. A 50 mEq sodium diet.

Intensive Diuretic Treatment. Spironolactone 400 mg/d plus furosemide 160 mg/d (bumetanide 4 mg/day or equivalent doses of other diuretics).

Early Ascites Recurrence. Reappearance of grade 2 to 3 ascites within 4 weeks of initial mobilization. Reaccumulation of ascites within 2 to 3 days of paracentesis must not be considered as early ascites recurrence because it represents a shift of interstitial fluid to the intraperitoneal space.

Diuretic-Induced Complications. Diuretic-induced hepatic encephalopathy is the development of hepatic encephalopathy in the absence of other precipitating factors. Diuretic-induced renal failure: increase in serum creatinine by greater than 100% to a value above 2 mg/dL in patients with ascites responding to diuretic treatment. Diuretic-induced hyponatremia: decrease in serum sodium concentration by greater than 10 mEq/L to a level lower than 125 mEq/L. Diuretic-induced hypo- or hyperkalemia: decrease of serum potassium concentration to less than 3 mEq/L or increase to more than 6 mEq/L despite appropriate measures to normalize potassium levels.

SPECIFIC CONDITIONS OTHER THAN REFRACTORY ASCITES

Recidivant Ascites. The ascites that recurs at least on three occasions within a 12-month period despite prescription of dietary sodium restriction and adequate diuretic dosage.

Ascites in Which Commencing Diuretic Treatment is Considered Inadvisable. The presence of acute hepatic encephalopathy or severe dilutional hyponatremia are considered contraindications to commencing diuretic therapy. However, no consensus was reached as to the degree of hyponatremia that would preclude the use of diuretics.

HISTORICAL AND CLINICAL ASPECTS OF HEPATORENAL SYNDROME

Historical Aspects. The presence of kidney dysfunction in patients with liver disease has been recognized for more than one century. One of the earliest reports of this association was made by Frerichs who in the ninteenth century described the existence of oliguria in patients with ascites.[93] In 1863, Austin Flint extended these observations and showed that in most cases renal failure in cirrhosis occurred in the absence of significant histological changes in the kidney at postmortem examination,[94] thus establishing the functional nature of this abnormality. The first detailed description of this syndrome, however, was not made until 1956 when Hecker and Sherlock reported nine patients with liver disease associated with renal failure characterized by lack of proteinuria and very low urinary sodium excretion.[95] These findings were subsequently confirmed in larger series of patients by several other groups. The functional nature of renal failure associated with liver disease was further established by studies showing that the kidneys of these patients could be successfully transplanted to patients with chronic renal failure and that renal failure was reversible after liver trans-

plantation.[96,97] Investigations performed during the 1960s and 1970s using clearance techniques and methods to evaluate the renal circulation showed that HRS is associated with marked renal vasoconstriction.[98,99] In these studies, it was also shown that this renal vasoconstriction is unique in that it occurs in the presence of an increased cardiac output and expanded plasma volume,[100] findings opposite to those observed in low-output cardiac failure and other types of prerenal azotemia. Over the last two decades most studies on HRS have been focused on the investigation of the vasoactive systems involved in the homeostasis of the renal circulation in cirrhosis. Schroeder et al[101] first described the existence of a markedly increased activation of the RAAS in patients with renal failure. The possible role of the SNS as a vasoconstrictor factor in the renal circulation in cirrhosis was first suggested by Ring-Larsen et al[102] and Arroyo et al.[54] A major breakthrough in the history of renal dysfunction in cirrhosis was the description of the crucial role of renal prostaglandins in the maintenance of renal perfusion. Boyer et al[57] first showed that the administration of NSAIDs to patients with cirrhosis and ascites caused a marked reduction in renal blood flow and GFR. Subsequent investigations confirmed these findings and raised the suggestion, still unproved, that renal failure in cirrhosis may be the consequence of reduced renal synthesis of vasodilator prostaglandins in the setting of increased activity of renal vasoconstrictor systems. Finally, recent investigations have been focused on the potential role of locally-synthesized vasoconstrictor substances, especially endothelin.[6]

Clinical Features. The term hepatorenal syndrome was first introduced to describe the renal failure that may follow biliary tract surgery.[103] Although it has been used anecdotally to designate different types of renal failure occurring in a variety of conditions involving the liver and the kidney, most recent studies have reserved this term to define the unique renal failure that develops in patients with cirrhosis, advanced liver failure, and severe sinusoidal portal hypertension. This renal failure is characterized by marked reduction of GFR because of renal vasoconstriction and is associated with severe sodium and water retention. Renal failure with characteristics similar to those of the HRS has also been described in patients with acute liver failure.[104]

Patients with cirrhosis show abnormalities in the systemic circulation during the course of their disease. In patients with compensated cirrhosis (i.e., without ascites) these abnormalities are characterized by increased plasma volume, reduced total systemic vascular resistance, and high cardiac output with normal arterial pressure.[61] As the disease progresses and patients develop renal sodium and water retention, the abnormalities in the arterial circulation become more marked and there is a tendency towards a reduction in arterial pressure.[105] Patients with HRS show the same hemodynamic pattern but with marked arterial hypotension.[105] All these circulatory changes occur despite a progressive stimulation of the SNS and RAAS and the nonosmotic release of ADH, indicating the existence of a gradual impairment in the arterial circulation as one progresses from compensated to decompensated cirrhosis and, finally, the HRS.[50]

Recent investigations using duplex-Doppler ultrasonography have found reduced brachial and femoral artery blood flows in patients with cirrhosis and HRS, indicating that arterial vasoconstriction in these patients is not exclusively restricted to the renal circulation.[105,106] These studies indirectly suggest that the main vascular bed responsible for arterial vasodilation and reduced total peripheral vascular resistance in cirrhosis is the splanchnic circulation.

In patients with cirrhosis, HRS may develop in two different clinical patterns.[107] In some patients, there is rapidly progressive reduction of GFR with a marked rise in blood urine nitrogen (BUN) and serum creatinine levels, often associated with marked oliguria, profound hyponatremia, and hyperkalemia. The prognosis of these patients is extremely poor.[108] Frequently, progressive renal failure appears to be triggered by complications, especially bacterial infections, gastrointestinal hemorrhage, major surgical procedures or acute alcoholic hepatitis. In other patients, there is a stable reduction of GFR with a moderate increase in BUN and serum creatinine levels that may persist for weeks or months. The survival of these patients is significantly longer than that of the former group. Most of these patients, however, eventually develop a rapidly progressive impairment of renal function as described above. These two types of patients show similar qualitative abnormalities in the arterial circulation as well as activation of endogenous vasoconstrictor systems. However, the abnormalities are more marked in the former group of patients. It is therefore very likely that both types of renal failure represent distinct expressions of the same pathogenic mechanism, that leads to a spectrum of renal disorders ranging from sodium retention to a rapidly progressive reduction of GFR.

PROPOSED DEFINITION AND DIAGNOSTIC CRITERIA OF HEPATORENAL SYNDROME IN CIRRHOSIS

Definition of Hepatorenal Syndrome

Hepatorenal syndrome is a syndrome that occurs 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. In the extrarenal circulation there is a predominance of arteriolar vasodilation, that results in reduction of total systemic vascular resistance and arterial hypotension. A similar syndrome may also occur in the setting of acute liver failure.

Hepatorenal syndrome may be classified on a clinical basis into two different clinical types: (1) type I hepato-

renal syndrome, characterized by rapidly progressive reduction of renal function as defined by a doubling of the initial serum creatinine to a level greater 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; and (2) type II hepatorenal syndrome, in which the renal failure does not have a rapidly progressive course.

Diagnostic Criteria

The proposed criteria for the diagnosis of the HRS in cirrhosis are listed in Table 2 and discussed below. Some of these criteria are considered major criteria and must be present for the diagnosis of HRS. The remaining criteria, most of them based on urinary indices, are not necessary for the diagnosis but may provide useful supportive evidence.

Major Criteria. One of the most difficult issues in the clinical evaluation of patients with cirrhosis is how to assess renal function because the standard methods used to estimate GFR are not very reliable in these patients. Serum creatinine is highly specific in the detection of low GFR but has a remarkably low-sensitivity.[109] This low-sensitivity is probably related to reduced endogenous production of creatinine because of protein malnutrition. Hence, a profound reduction in GFR is necessary to increase serum creatinine levels over the accepted normal levels for patients without liver disease. BUN is more sensitive than serum creatinine and also has a high-specificity.[109] However, BUN levels may be lower than expected in patients with liver disease because of reduced hepatic synthesis of urea. On the other hand, BUN may increase for reasons other than reduced GFR, i.e., gastrointestinal hemorrhage or catabolic states. Finally, the sensitivity of 24-hour creatinine clearance is probably higher than that of BUN or serum creatinine levels. The main problems with this method, however, are that it may overestimate GFR, especially in patients with renal failure, and requires a very accurate 24-hour urine collection.[110]

Ideally, therefore, GFR in patients with liver disease should be estimated by very precise methods (i.e., inulin, [^{125}I]iothalamate or ^{51}Cr-EDTA clearance). Nevertheless, because this approach is not feasible in most clinical settings, the criteria proposed to establish a significant reduction in GFR in these patients are the following: (1) serum creatinine of greater than 1.5 mg/dL; or (2) 24-hour creatinine clearance of less than 40 mL/min, providing an accurate urine collection is ensured.

These criteria are highly specific but may have a relatively low-sensitivity. In patients at high risk of developing renal failure frequent measurement of these parameters may be useful to detect progressive reductions of GFR. By contrast, in studies investigating the pathophysiology or treatment of renal dysfunction in patients with liver diseases, the use of more accurate techniques to estimate GFR (i.e., inulin clearance, [^{125}I]iothalamate or ^{51}Cr-EDTA clearance) is mandatory.

Patients with cirrhosis are frequently exposed to a variety of clinical situations that may predispose to renal failure different from HRS. These conditions have to be excluded before the diagnosis of HRS is made.

Gastrointestinal bleeding and bacterial infections are frequent complications of patients with cirrhosis that may lead to the development of shock (decrease in arterial pressure associated with reduction of tissue perfusion) that if prolonged, can cause acute renal failure because of acute tubular necrosis (ATN). The characteristics of ATN in these patients are similar to those of ATN in patients without liver disease. However, it should be taken into account that some patients with HRS may eventually develop ATN because of intense renal vasoconstriction and subsequent renal ischemia.[111]

Recently, it has been shown that approximately one third of cirrhotic patients with spontaneous bacterial peritonitis develop renal impairment in close chronological relationship with the onset of infection.[112] This renal impairment is reversible in almost one third of cases after successful treatment with third generation cephalosporins. Therefore, an ongoing bacterial infection should be excluded in cirrhotic patients with renal failure. Several drugs are known to induce renal failure in patients with cirrhosis. Among them, the most important in clinical practice are NSAIDs,[57] aminoglycosides,[113] and diuretics.[75] NSAIDs have been reported to cause renal failure in patients with cirrhosis and ascites by inhibiting renal prostaglandin synthesis. In ad-

TABLE 2. International Ascites Club's Diagnostic Criteria of Hepatorenal Syndrome

Major Criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dL or 24-h creatinine clearance <40 mL/min.
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss >500 g/d for several days in patients with ascites without peripheral edema or 1,000 g/d in patients with peripheral edema).
No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.
Additional Criteria
Urine volume <500 mL/d.
Urine sodium <10 mEq/L.
Urine osmolality greater than plasma osmolality.
Urine red blood cells <50 per high power field.
Serum sodium concentration <130 mEq/L.

dition, patients with cirrhosis are predisposed to develop ATN during treatment with aminoglycosides, particularly when these drugs are given in combination with cephalotin. Finally, as stated before, the administration of inappropriately high doses of diuretics may lead to prerenal failure, especially in patients without peripheral edema.[79,114]

Prerenal failure may also be found in patients with cirrhosis when there is depletion of intravascular volume because of significant gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses because of aggressive diuretic therapy (weight loss greater than 500 g/d for several days in patients with ascites without peripheral edema or 1,000 g/d in patients with peripheral edema). This situation is characterized by reduced renal perfusion and low GFR and is rapidly reversible after restoration of intravascular volume with plasma expanders. By contrast, no significant changes in renal function are observed in patients with HRS after plasma volume expansion.[115] To exclude any possible role of subtle reductions in plasma volume as cause of renal failure, renal function should be evaluated after diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline. If there is no sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) after this maneuver, the diagnosis of HRS is made. Only in the few cases in whom there is a high index of clinical suspicion of intravascular volume depletion, renal function may be evaluated after normalizing central venous pressure or pulmonary capillary wedge pressure with plasma volume expansion.

Because no significant glomerular or tubular damage exists in HRS, proteinuria is usually absent. The presence of significant proteinuria (greater than 500 mg/d) in patients with cirrhosis and renal failure is, therefore, highly suggestive of glomerular disease. In this regard, it is important to remark that glomerular lesions because of deposition of immunecomplexes sufficient enough to cause renal failure are not uncommon in patients with alcohol-induced liver disease or chronic hepatitis B or C virus infection.[116-118]

Additional Criteria. Urine volume in patients with HRS is usually lower than 500 mL/d. However, as is the case with other types of acute renal failure, there are rare nonoliguric forms of the syndrome.

Diseases causing prerenal failure are usually characterized by a normal sodium reabsorptive capacity as opposed to ATN in which the ability to reabsorb sodium in the renal tubules is impaired. Urinary sodium concentration is, therefore, low in the former group ($<$10 mEq/L) and high ($>$20 mEq/L) in the latter. In HRS, the function of the renal tubules is preserved and urine sodium is usually lower than 10 mEq/L. However, sporadic cases of patients with urine sodium higher than 10 mEq/L and otherwise well-documented HRS have been reported.[119] On the other hand, cirrhotic patients with superimposed ATN may have low urine sodium.[113]

Because urinary concentration capacity is preserved in patients with HRS, urine osmolality is generally higher than plasma osmolality. Nevertheless, in some patients a decrease in urine osmolality may be observed as renal failure progresses.

Examination of urine sediment is of value in the diagnosis of renal failure. Patients with HRS generally do not have hematuria and the existence of significant hematuria makes the diagnosis of HRS very unlikely and points strongly towards the existence of glomerular disease as the cause of renal failure, especially when proteinuria is present.

An impaired renal capacity to excrete free water is almost a universal finding in cirrhotic patients with HRS. In most of these patients, this disorder is associated with dilutional hyponatremia, that in some cases may be severe.

CONCLUSION

Refractory ascites and hepatorenal syndrome frequently complicate the natural history of cirrhotic patients with ascites. Despite this high frequency, there has been great variability regarding the definition and diagnostic criteria of these syndromes. This study reports the conclusions reached at a Consensus Conference organized to discuss these topics. It should be emphasized that the limited information on several clinical and therapeutic aspects of these complications made the delineation of diagnostic criteria difficult. The proposed definitions and diagnostic criteria should, therefore, stimulate prospective studies to increase our understanding on clinical and pathophysiological aspects of these complications. Also, they should be useful in the design of clinical trials of new approaches in the management of these complications.

REFERENCES

1. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arteriolar vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. HEPATOLOGY 1988;8:1151-1157.
2. Simonson MS. Endothelins: multifunctional renal peptides. Physiol Rev 1993;73:375-411.
3. Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43: 109-142.
4. Bomzon A, Blendis LM. The nitric oxide hypothesis and the hyperdynamic circulation in cirrhosis. HEPATOLOGY 1994;20: 1343-1350.
5. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide. Lancet 1991;337:776-778.
6. Moore K, Wendon J, Frazer M, Karani J, Williams R, Badr K. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. N Engl J Med 1992;327:1774-1778.
7. Ginès P, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, Rimola A, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology 1987;92:234-241.
8. Ferral H, Bjarnason H, Wegryn SA, Rengel GJ, Nazarian GK, Rank JM, Tadavarthy SM, et al. Refractory ascites: early experience in the treatment with transjugular intrahepatic portosystemic shunt. Radiology 1993;189:795-801.
9. Clària J, Jiménez W, Arroyo V, Guarner F, López C, LaVilla G, Asbert M, et al. Blockade of the hydroosmotic effect of vasopressin normalizes water excretion in cirrhotic rats. Gastroenterology 1989;97:1294-1299.

10. Tsuboi Y, Ishikawa SE, Fujisawa G, Okada K, Saito T. Therapeutic efficacy of the non-peptide AVP antagonist OPC-31260 in cirrhotic rats. Kidney Int 1994;46:237-244.
11. Bosch-Marcé M, Jiménez W, Angeli P, Leivas A, Clària J, Graziotto A, Arroyo V, et al. Aquaretic efficacy of the kappa opioid agonist RU 51599 in cirrhotic rats with ascites and water retention. Gastroenterology 1995;109:217-223.
12. Llovet JM, Bartoli R, Planas R, Cabré E, Jiménez W, Urban A, Ojanguren J, et al. Bacterial translocation in cirrhotic rats. Its role in the development of SBP. Gut 1994;35:1648-1652.
13. Byl B, Roucloux I, Crusiaux A, Dupont E, Devière J. Tumor necrosis factor alpha and interleukin-6 plasma levels in infected cirrhotic patients. Gastroenterology 1993;104:1492-1497.
14. Arroyo V, Navasa M, Rimola A. Spontaneous bacterial peritonitis in cirrhosis. Treatment and prophylaxis. Infection 1994;22 (suppl 3):167S-175S.
15. Ginès P, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forné M, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. HEPATOLOGY 1990;12:716-724.
16. Soriano G, Guarner C, Teixidó M, Such J, Barrios J, Enriquez J, Vilardell J. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology 1991;100: 477-481.
17. Earley LE. Presentation of diagnostic criteria of the hepatorenal syndrome. In: Bartoli E, Chiandussi L, eds. Hepatorenal Syndrome. Padova: Piccin Medical Books, 1979:495-504.
18. Arroyo V, Epstein M, Gallus G, Gentilini P, Ring-Larsen H, Salerno F. Refractory ascites in cirrhosis. Mechanism and management. Gastroenterology Int 1989;2:195-207.
19. Arroyo V, Ginès A, Saló J. A European survey on the treatment of ascites in cirrhosis. J Hepatol 1994;21:667-672.
20. Czaja AJ. Chronic active hepatitis: the challenge for a new nomenclature. Ann Intern Med 1993;119:510-517.
21. Bernardi M, Di Marco C, Trevisani F, Fornalé L, Andreone P, Cursaro C, Baraldini M, et al. Renal sodium retention during upright posture in preascitic cirrhosis. Gastroenterology 1993;105:188-193.
22. Bernardi M, Trevisani F, Gasbarrini A, Gasbarrini G. Hepatorenal disorders: role of the renin-angiotensin-aldosterone system. Semin Liver Dis 1994;14:23-34.
23. Pérez-Ayuso RM, Arroyo V, Planas R, Gaya J, Bory F, Rimola A, Rivera F, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. Gastroenterology 1983;84:961-968.
24. Henriksen JH, Ring-Larsen H. Hepatorenal disorders: role of the sympathetic nervous system. Semin Liver Dis 1994;14:35-43.
25. Nicholls KM, Shapiro MD, Van Putten VJ, Kluge R, Chung HM, Bichet DG, Schrier RW. Elevated plasma norepinephrine concentrations in decompensated cirrhosis. Association with increased secretion rates, normal clearance rates, and suppressibility by central blood volume expansion. Circ Res 1985; 56:457-461.
26. Willett I, Esler M, Burke F, Leonard P, Dudley F. Total and renal sympathetic nervous system activity in alcoholic cirrhosis. J Hepatol 1985;1:639-648.
27. Esler M, Dudley F, Jennings G, Debinski H, Lambert G, Jones P, Crotty B, et al. Increased sympathetic nervous activity and the effects of its inhibition with clonidine in alcoholic cirrhosis. Ann Intern Med 1992;116:446-455.
28. Floras JS, Legault L, Morali GA, Hara K, Blendis LM. Increased sympathetic outflow in cirrhosis and ascites: direct evidence from intraneural recordings. Ann Intern Med 1991; 114:373-380.
29. Henriksen JH, Ring-Larsen H, Kanstrup IL, Christensen NJ. Splanchnic and renal elimination and release of catecholamines in cirrhosis. Evidence of enhanced sympathetic nervous activity in patients with decompensated cirrhosis. Gut 1984;25:1034-1043.
30. Henriksen JH, Ring-Larsen H, Christensen NJ. Hepatic intestinal uptake and release of catecholamines in alcoholic cirrhosis. Evidence of enhanced hepatic intestinal sympathetic nervous activity. Gut 1987;28:1637-1642.
31. Kopeke JP, Jones S, DiBona GF. Renal nerves mediate blunted natriuresis to atrial natriuretic peptide in cirrhotic rats. Am J Physiol 1987;252:R1019-R1023.
32. DiBona GF, Herman PJ, Sawin LL. Neural control of renal function in edema-forming states. Am J Physiol 1988;254: R1017-R1024.
33. DiBona GF, Sawin LL. Role of renal nerves in sodium retention of cirrhosis and congestive heart failure. Am J Physiol 1991;260:R298-R305.
34. Rodríguez-Martínez M, Sawin LL, DiBona GF. Arterial and cardiopulmonary baroreflex control of renal nerve activity in cirrhosis. Am J Physiol 1995;268:R117-R129.
35. Saló J, Ginès A, Anibarro L, Jiménez W, Clària J, Ginès P, Rivera F, et al. Effect of upright posture and physical exercise on endogenous neurohormonal systems in cirrhotic patients with sodium retention and normal supine plasma renin, aldosterone and norepinephrine levels. HEPATOLOGY 1995;22:479-487.
36. Atucha N, Cegarra M, Ramírez A, Quesada T, Garcia-Estañ J: Pressure diuresis and natriuresis in cirrhotic rats. Am J Physiol 1993;265:G1045-G1049.
37. Wong F, Blendis L. Pathophysiology of sodium retention and ascites formation in cirrhosis: role of atrial natriuretic factor. Semin Liver Dis 1994;14:59-70.
38. Arroyo V, Clària J, Saló J, Jiménez W. Antidiuretic hormone and the pathogenesis of water retention in cirrhosis with ascites. Semin Liver Dis 1994;14:44-58.
39. Camps J, Solá J, Arroyo V, Pérez-Ayuso RM, Gaya J, Rivera F, Rodés J. Temporal relationship between the impairment of free water excretion and antidiuretic hormone hypersecretion in rats with experimental cirrhosis. Gastroenterology 1987;93: 498-505.
40. Ginès P, Abraham W, Schrier RW. Vasopressin in pathophysiological states. Semin Nephrol 1994;14:384-97.
41. Bichet DG, Van Putten VJ, Schrier RW. Potential role of increased sympathetic activity in impaired sodium and water excretion in cirrhosis. N Engl J Med 1982;307:1552-1557.
42. Pérez-Ayuso RM, Arroyo V, Camps J, Rimola A, Gaya J, Costa J, Rivera F, et al. Evidence that renal prostaglandins are involved in renal water metabolism in cirrhosis. Kidney Int 1984;26:72-80.
43. Bichet D, Szatalowicz V, Chaimovitz C, Schrier RW: Role of vasopressin in abnormal water excretion in cirrhotic patients. Ann Intern Med 1982;96:413-417.
44. Asahina Y, Izumi N, Enomoto N, Sasaki S, Fushimi K, Marumo F, Sato C. Increased gene expression of water channel in cirrhotic rat kidneys. HEPATOLOGY 1995;21:169-173.
45. Linas SL, Anderson RJ, Guggenheim SJ, Robertson GL, Berl T. Role of vasopressin in impaired water excretion in conscious rats with experimental cirrhosis. Kidney Int 1981;20:173-180.
46. Kim JK, Summer SN, Howard RL, Schrier RW. Vasopressin gene expression in rats with experimental cirrhosis. HEPATOLOGY 1993;17:143-147.
47. Solís-Herruzo JA, González-Gamarra A, Castellano G, Muñoz-Yagüe MT. Metabolic clearance rate of arginine vasopressin in patients with cirrhosis. HEPATOLOGY 1992;16:974-979.
48. DiBona GF. Renal neural activity in hepatorenal syndrome. Kidney Int 1984;25:841-853.
49. Arroyo V, Ginès P, Jiménez W, Rodés J. Ascites, renal failure, and electrolyte disorders in cirrhosis. Pathogenesis, diagnosis, and treatment. In: McIntyre N, Benhamou JP, Bircher J, Rizetto M, Rodés J, ed. Textbook of Clinical Hepatology. Ed 1. Oxford: Oxford Medical Press, 1991:429-470.
50. Schrier RW, Neiderbeger M, Weigert A, Ginès P. Peripheral arterial vasodilation: determinant of functional spectrum of cirrhosis. Semin Liv Dis 1994;14:14-22.
51. Henriksen JH, Ring-Larsen H, Christensen NJ. Autonomic nervous function in liver disease. In: Bomzon A, Blendis LM, eds.

Cardiovascular complications of liver disease. Ed 1. Boca Raton: CRC Press, 1990:63-79.
52. Solís-Herruzo JA, Durán A, Favela V, Castellano L, Madrid L, Muñoz-Yagüe MT, Morillas JD, et al. Effects of lumbar sympathetic block on kidney function in cirrhotic patients with hepatorenal syndrome. J Hepatol 1987;5:167-173.
53. Zipser RD, Hoefs JC, Speckart PF, Zia PK, Horton R: Prostaglandins: modulators of renal function and pressor resistance in chronic liver disease. J Clin Endocrinol Metab 1979;8:895-900.
54. Arroyo V, Planas R, Gaya J, Deulofeu R, Rimola A, Pérez-Ayuso RM, Rivera F, et al. Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin E2 in cirrhosis. Relationship to functional renal failure and sodium and water excretion. Eur J Clin Invest 1983;13:271-278.
55. Rimola A, Ginès P, Arroyo V, Camps J, Pérez-Ayuso RM, Quintero E, Gaya J, et al. Urinary excretion of 6-keto-prostaglandin F1- alpha, thromboxane B2 and prostaglandin E2 in cirrhosis with ascites. Relationship to functional renal failure (hepatorenal syndrome). J Hepatol 1986;3:111-117.
56. Govindarajan S, Nast CC, Smith WL, Koyle MA, Daskalopoulos J, Zipser RD. Immunohistochemical distribution of renal prostaglandin endoperoxide synthase and prostacyclin synthase: diminished endoperoxide synthase in the hepatorenal syndrome. HEPATOLOGY 1987;7:654-659.
57. Boyer TD, Zia P, Reynolds TB. Effects of indomethacin and prostaglandin A1 in renal function and plasma renin activity in alcoholic liver disease. Gastroenterology 1979;77:215-222.
58. Arroyo V, Ginès P, Rimola A, Gaya J. Renal function abnormalities, prostaglandins, and effects of nonsteroidal anti-inflammatory drugs in cirrhosis with ascites. An overview with emphasis on pathogenesis. Am J Med 1986;81:104-122.
59. Ros J, Clària J, Jiménez W, Bosch M, Angeli P, Arroyo V, Rivera F, et al. Role of nitric oxide and prostacyclin in the control of renal perfusion in experimental cirrhosis. HEPATOLOGY 1995; 22:915-920.
60. Angeli P, Jiménez W, Arroyo V, Mackenzie HS, Zhang PL, Clària J, Rivera F, et al. Renal effects of endogenous natriuretic peptides receptor blockade in cirrhotic rats with ascites. HEPATOLOGY 1994;20:948-954.
61. Bosch J, Arroyo V, Betriu A, Mas A, Carrilho F, Rivera F, Navarro-lópez F, et al. Hepatic hemodynamics and the renin-angiotensin-aldosterone system in cirrhosis. Gastroenterology 1980;78:92-99.
62. Castells A, Saló J, Planas R, Quer JC, Ginès A, Boix J, Ginès P, et al. Impact of shunt surgery for variceal bleeding in the natural history of ascites in cirrhosis: a retrospective study. HEPATOLOGY 1994;20:584-591.
63. Witte CL, Witte MH, Dumont AE. Lymph imbalance in the genesis and perpetuation of the ascites syndrome in hepatic cirrhosis. Gastroenterology 1980;78:1059-1068.
64. Lieberman FL, Denison EK, Reynolds TB. The relationship of plasma volume, portal hypertension, ascites and renal sodium retention in cirrhosis. The "overflow" theory of ascites formation. Ann N Y Acad Sci 1970;170:202-212.
65. Kostreva DR, Castañer A, Kampine JP. Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nerve activity. Am J Physiol 1980;238:R390-R394.
66. Arroyo V, Ginès P. Arteriolar vasodilation and the pathogenesis of the hyperdynamic circulation and renal sodium and water retention in cirrhosis. Gastroenterology 1992;102:1077-1079.
67. Karim A. Spironolactone: disposition, metabolism, pharmacodynamics and bioavailability. Drug Metab Rev 1978;8:151-158.
68. Sungaila I, Bartle WR, Walker SE, DeAngelis CD, Uetrecht J, Pappas C, Vidins E. Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. Gastroenterology 1992;102:1680-1685.
69. Funder JW. Aldosterone action. Annu Rev Physiol 1993;55:115-130.
70. Gatta A, Angeli P, Caregaro L, Menon F, Sacerdoti D, Merkel C. A pathophysiological interpretation of unresponsiveness to spironolactone in a stepped-care approach to the diuretic treatment of ascites in nonazotemic cirrhotic patients. HEPATOLOGY 1991;14:231-236.
71. Puschett JB, Winaver J. Effects of diuretics on renal function. In: Windhager EE, ed. Handbook of Physiology, Section 8, Renal Physiology. New York: Oxford University Press, 1992:2335-2406.
72. Attallah AA. Interaction of prostaglandins with diuretics. Prostaglandins 1979;18:369-375.
73. Pinzani M, Daskalopoulos G, Laffi G, Gentilini P, Zipser RD. Altered furosemide pharmacokinetics in chronic alcoholic liver disease with ascites contributes to diuretic resistance. Gastroenterology 1987;92:294-298.
74. Gerbes AL, Bertheau-Reitha U, Falkner C, Jüngst D, Paumgartner G. Advantages of the new loop diuretic torasemide over furosemide in patients with cirrhosis and ascites. A randomized, double-blind cross-over trial. J Hepatol 1993;17:353-358.
75. Sherlock S, Senewiratne B, Scott A, Walker JG. Complications of diuretic therapy in hepatic cirrhosis. Lancet 1966;1:1049-1053.
76. Strauss E, De Sa MG, Lacet CMC, Cartapatti Da Silva E, Dos Santos WR, Honain NZ, Maffei RA Jr. Standardization of a therapeutic approach for ascites due to chronic liver disease. A prospective study of 100 cases. GED 1985;4:79-86.
77. Baerltl JM, Sancetta SM, Gabuzda GJ. Relation to acute potassium depletion to renal ammonium metabolism in patients with cirrhosis. J Clin Pharmacol 1963;42:696-707.
78. Häussinger D. Organization of hepatic nitrogen metabolism and its relation to acid-base homeostasis. Klin Wochenschr 1990;68:1096-1101.
79. Shear L, Ching S, Gabuzda GJ. Compartmentalization of ascites and edema in patients with hepatic cirrhosis. N Engl J Med 1970;282:1391-1396.
80. Campra JL, Reynolds TB. Effectiveness of high-dose spironolactone therapy in patients with chronic liver disease and relatively refractory ascites. Dig Dis Sci 1978;23:1025-1030.
81. Gabow PA, Moore S, Schrier RW. Spironolactone induced hyperchloremic acidosis in cirrhosis. Ann Intern Med 1979;90: 338-340.
82. Salerno F, Badalamenti S, Tempini S, Restell B, Bruno S, Belati G, Roffi L. Repeated paracentesis and i.v. albumin infusion to treat tense ascites in cirrhotic patients. J Hepatol 1987;5:102-108.
83. Titó LI, Ginès P, Arroyo V, Planas R, Panés J, Rimola A, Llach J, et al. Total paracentesis associated with intravenous albumin in the management of cirrhosis and ascites. Gastroenterology 1990;98:146-152.
84. Campbell P, Blendis LM. Physiological consequences of peritoneovenous shunting (PVS) in patients with refractory ascites secondary to chronic liver disease: implications for the pathogenesis of ascites. J Clin Nutr Gastroenterol 1986;1:159-166.
85. Ginès P, Arroyo V, Vargas V, Planas R, Casafont F, Panés J, Hoyos M, et al. Paracentesis with infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med 1991;325:829-835.
86. Clowdus BF, Higgins JA, Rosevear JW, Summerskill WHJ. Treatment of "refractory" ascites with a new aldosterone antagonist in patients with cirrhosis. Proc Staff Meet Mayo Clin 1960;35:97-105.
87. Franco D, Vons C, Traynor O, de Smadja C. Should portosystemic shunt be reconsidered in the treatment of intractable ascites in cirrhosis? Arch Surg 1988;123:987-991.
88. Eknoyan G, Martinez-Maldonado M, Yium JJ, Suki WN. Combined ascitic-fluid and furosemide infusion in the management of ascites. N Engl J Med 1970;282:713-717.
89. Levi VG, Opolon P, Pauleau N, Caroli J. Treatment of ascites by reinfusion of concentrated peritoneal fluid: review of 318 procedures in 210 patients. Postgrad Med J 1975;51:564-566.
90. Raju SF, Achord JL. The effect of dialytic ultrafiltration and peritoneal reinfusion in the management of diuretic resistant ascites. Am J Gastroenterol 1984;79:308-312.
91. LeVeen HH, Christoudias G, Ip M, Luft R, Falk G, Grosberg S. Peritoneo-venous shunting for ascites. Ann Surg 1974;180:580-590.

92. Bernardi M, Laffi G, Salvagnini M, Azzena G, Bonato S, Marra F, Trevisani F, et al. Efficacy and safety of the stepped care medical treatment of ascites in liver cirrhosis: a randomized controlled clinical trial comparing two diets with different sodium content. Liver 1993;13:156-162.
93. v Frerichs T. Tratado Práctico de las Enfermedades del Hígado, de los Vasos Hepáticos y de las Vias Biliares. Madrid: Librería Extranjera y Nacional, científica y Literaria, 1877, 362-353.
94. Flint A. Clinical report on hydro-peritoneum based on an analysis of forty-six cases. Am J Med Sci 1863;45:306-339.
95. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet 1956;2:1221-1225.
96. Koppel MH, Coburn JN, Mims MM, Goldtein H, Boyle H, Rubini ME. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome. Evidence for the functional nature of renal failure in advanced liver disease. N Engl J Med 1969;280:1367-1371.
97. Iwatsuki S, Popovtzer MM, Corman JL, Ishikawa M, Putnam CW, Katz FH, Starzl TE. Recovery from hepatorenal syndrome after orthotopic liver transplantation. N Engl J Med 1973;289:1155-1159.
98. Schroeder ET, Shear L, Sancetta SM, Gabuzda JG. Renal failure in patients with cirrhosis of the liver. III Evaluation of intrarenal blood flow by para-aminohippurate extraction and response to angiotensin. Am J Med 1967;43:887-896.
99. Epstein M, Berk DP, Hollenberg NK, Adams DF, Chalmers TC, Abrams HL, Merrill JP. Renal failure in the patient with cirrhosis. The role of active vasoconstriction. Am J Med 1970;49:175-185.
100. Tristani FE, Cohn JN. Systemic and renal hemodynamics in oliguric hepatic failure: effect of volume expansion. J Clin Invest 1967;46:1894-1906.
101. Schroeder ET, Eich RH, Smulyan H, Gould AB, Gabuzda GJ. Plasma renin levels in hepatic cirrhosis. Relationship to functional renal failure. Am J Med 1970;49:186-191.
102. Ring-Larsen H, Hesse B, Henriksen JH, Christensen NJ. Sympathetic nervous activity and renal and systemic hemodynamics in cirrhosis: plasma norepinephrine concentration, hepatic extraction, and renal release. HEPATOLOGY 1982;2:304-310.
103. Helwig FC, Schulltz CB. A liver kidney syndrome. Clinical, pathological and experimental studies. Surg Gynecol Obstet 1932;55:570-580.
104. Wilkinson S, Arroyo V, Gazzard BG, Moodie H, Williams R. Relation of renal impairment and haemorrhagic diathesis to endotoxaemia in fulminant hepatic failure. Lancet 1974;1:521-524.
105. Fernández-Seara J, Prieto J, Quiroga J, Zozaya JM, Cobos MA, Rodríguez-Eire J, García-Plaza A, et al. Systemic and regional hemodynamics in patients with liver cirrhosis with and without functional renal failure. Gastroenterology 1989;97:1304-1312.
106. Maroto A, Ginés P, Arroyo V, Ginés A, Saló J, Clària J, Jiménez W, et al. Brachial and femoral artery blood flow in cirrhosis: relationship to kidney dysfunction. HEPATOLOGY 1993;17:788-793.
107. Rodés J, Bosch J, Arroyo V. Clinical types and drug therapy of renal impairment in cirrhosis. Postgrad Med J 1975;51:492-497.
108. Ginès A, Escorsell A, Ginès P, Saló J, Jiménez W, Inglada L, Navasa M, et al. Incidence, predictive factors and prognosis of hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229-236.
109. Maroto A, Ginès A, Saló J, Clària J, Ginès P, Anibarro L, Jiménez W, et al. Diagnosis of functional kidney failure of cirrhosis with Doppler sonography: prognostic value of resistive index. HEPATOLOGY 1994;20:839-844.
110. Schuster VL, Seldin DW. Renal Clearance. In: Seldin DW, Giebisch G, eds. The Kidney: Physiology and Pathophysiology. Second Edition. New York: Raven, 1992:943-978.
111. Mandal AK, Lansing M, Fahmy A. Acute tubular necrosis in hepatorenal syndrome: an electron microscopy study. Am J Kidney Dis 1982;2363-2374.
112. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, et al. Renal impairment following spontaneous bacterial peritonitis in cirrhosis. Incidence, clinical course, predictive factors and prognosis. HEPATOLOGY 1994;20:1495-1501.
113. Cabrera J, Arroyo V, Ballesta AM, Rimola A, Gual J, Elena M, Rodés J. Aminoglycoside nephrotoxicity in cirrhosis. Value of urinary beta-2-microglobulin to discriminate functional renal failure from acute tubular damage. Gastroenterology 1982;82:97-105.
114. Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral edema. Gastroenterology 1986;90:1827-1833.
115. Linas SL, Schaefer JW, Moore EE, Good JT Jr, Giansiracusa R. Peritoneovenous shunt in the management of the hepatorenal syndrome. Kidney Int 1986;30:736-740.
116. Newell GC. Cirrhotic glomerulonephritis: incidence, morphology, clinical features, and pathogenesis. Am J Kidney Dis 1987;9:183-190.
117. Nagy J, Bajtai G, Brasch H, Süle T, Ambrus M, Deák G, Hámori A. The role of hepatitis B surface antigen in the pathogenesis of glomerulonephritis. Clin Nephrol 1979;12:109-116.
118. Johnson RJ, Gretch DR, Yamabe Y, Hart J, Bacchi CE, Hartwell P, Couser WG, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med 1993;328:465-470.
119. Dudley FJ, Kanel GC, Wood LJ, Reynolds TB. Hepatorenal syndrome without avid sodium retention. HEPATOLOGY 1986;6:248-251.