World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i5.251

World J Hepatol 2013 May 27; 5(5): 251-263
ISSN 1948-5182 (online)

REVIEW

Cirrhotic ascites review: Pathophysiology, diagnosis and management

Christopher M Moore, David H Van Thiel

Christopher M Moore, David H Van Thiel, Section of Hepatology, Department of Medicine, Rush University Medical Center, Chicago, IL 60612, United States

Author contributions: Moore CM contributed to conception, drafting and revision, and final approval of this article; Van Thiel DH contributed to the conception, drafting and revision, and final approval of this article.

Correspondence to: Christopher M Moore, MD, Section of Hepatology, Department of Medicine, Rush University Medical Center, 1725 W Harrison St, Chicago, IL 60612, United States. christopher_moore@rush.edu
Telephone: +1-312-9425861 Fax: +1-312-5633945
Received: February 16, 2013 Revised: April 13, 2013
Accepted: April 18, 2013
Published online: May 27, 2013

Abstract

Ascites is a pathologic accumulation of peritoneal fluid-commonly observed in decompensated cirrhotic states. Its causes are multi-factorial, but principally involve significant volume and hormonal dysregulation in the setting of portal hypertension. The diagnosis of ascites is considered in cirrhotic patients given a constellation of clinical and laboratory findings, and ultimately confirmed, with insight into etiology, by imaging and paracentesis procedures. Treatment for ascites is multimodal including dietary sodium restriction, pharmacologic therapies, diagnostic and therapeutic paracentesis, and in certain cases transjugular intra-hepatic portosystemic shunt. Ascites is associated with numerous complications including spontaneous bacterial peritonitis, hepato-hydrothorax and hepatorenal syndrome. Given the complex nature of ascites and associatedcomplications, it is not surprising that it heralds increased morbidity and mortality in cirrhotic patients and increased cost-utilization upon the health-care system. This review will detail the pathophysiology of cirrhotic ascites, common complications derived from it, and pertinent treatment modalities.

Key words: Ascites; Cirrhosis; Hepato-hydrothorax; Hepatorenal syndrome; Spontaneous bacterial peritonitis

Core tip: Ascites is an accumulation of fluid most commonly found in cirrhosis with portal hypertension. Ascites can cause or is associated with a number of complications including spontaneous bacterial peritonitis, hepato-hydrothorax and hepatorenal syndrome. Ascites itself, and these associated complications are a significant cause of morbidity and mortality in cirrhotic patients. The management of ascites is complex, utilizing an array of medications and interventional therapies to maintain appropriate total body volume, prevent multi-organ dysfunction, and manage against increased risk for associated infections.

Moore CM, Van Thiel DH. Cirrhotic ascites review: Pathophysiology, diagnosis and management. *World J Hepatol* 2013; 5(5): 251-263 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i5/251.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i5.251

INTRODUCTION

Ascites is a very common manifestation of decompensated cirrhosis and represents a pathologic accumulation of fluid within the peritoneal cavity[1-3]. The term "ascites" is derived from the Greek term "*askos*" in reference to its similar appearance to a winebag or sac. This seems rather appropriate, both in description of presentation and as an allusion to a main cause of cirrhosis. The term "ascitic fluid" is also utilized in the literature however it is in a way redundant. The clinical presentation of ascites has been described since antiquity, reasonably inferred from passages in the Egyptian medical text, the *Ebers Papyrus* c. 1550 BCE[4].

Cirrhotic ascitic fluid accumulation results from a

number of factors broadly defined in terms of hormonal and cytokine dysregulation and related volume overload in the setting of portal hypertension[1]. The manifestation of ascites is an important landmark in the progression of cirrhosis: (1) it is the most common cause for hospital admissions and thus contingent costs; (2) it portends increased 1-year mortality; and (3) functions as a risk-stratification marker for orthotopic liver transplantation (OLT)[1,5-7]. This review will characterize the pathophysiology of cirrhotic ascitic fluid formation, the complications surrounding ascites, and basic medical management of these processes.

PATHOPHYSIOLOGY

For the purposes of this discussion, the focus will be on cirrhotic ascites, in the setting of portal hypertension, which comprises approximately 85% of all cases[1,2,5]. Other causes of ascites (non-cirrhotic)can be broadly defined as pre- or post-hepatic in origin. Pre-hepatic causes might include: portal vein thrombosis, lymphoma, abdominal lymphatic injury or obstruction, bowel perforation, renal failure, pancreatitis, peritoneal tuberculosis, or a malignancy with peritoneal implants. Post-hepatic causes include congestive heart failure usually associated with pulmonary hypertension, constrictive pericarditis, the Budd-Chiari syndrome, and stricture/web formation in the inferior vena cava (IVC)[1,5]. This latter category, regarding IVC stricture/web formation, is likely to manifest rather slowly overtime as obstruction to critical flow progresses.

Malignant ascites, which is found in 10% of cases, can occur as a result of any neoplastic disease having peritoneal metastasis, but is more common with breast, bronchus, ovary, gastric, pancreatic or colon cancer. Up to 20% of cases of malignant ascites have a tumor of unknown origin. Most cases of malignant ascites have a high protein content[8-10]. Because there are multiple potential causes of ascites other than liver disease and/or portal hypertensive origin, non-hepatic disease processes should be ruled out through clinical history and by utilizing specific laboratory testing and imaging. As an example, in the setting of chronic pancreatitis with associated pseudocyst and internal fistulae formation, significant fluid can directly enter into the peritoneal cavity and manifest as abdominal distension with pain. In particular an elevated ascitic fluid amylase level, found on diagnostic paracentesis, is strongly diagnostic for this category. The physician might be especially sensitive to this diagnosis in a patient with a significant history of alcohol use, chronic pancreatitis and steatorrhea. Notably, the serum-ascites albumin gradient (SAAG) is a useful tool for segregating ascites-associated disease processes due to portal hypertension, such as cirrhosis, from the many other non-portal hypertensive causes of ascites[11]. A SAAG value $\geqslant$ 1.1 g/dL strongly supports (97% sensitivity) a diagnosis of portal hypertension as causal[11].

Despite its well known presentation, the pathogenesis of ascites remains incompletely understood and continues to evolve. A hybrid theory currently prevails, having arisen out of the "overflow" and "underfill" theories of the past generation[1,2,5]. A brief sketch of these views suggests the following: (1) continuous injury to the liver as a combination of both exogenous factors, *e.g.*, chronic alcohol or viral or non-alcoholic steatohepatitis (NASH) injury; (2) in the setting of an appropriate genetic disposition; and (3) continued micro-processes of inflammation, necrosis and collagen deposition/regeneration, all conspiring to transform the liver from a low-resistance to a high-resistance system, *e.g.*, a spectrum of fibrosis with vascular smooth muscle dysfunction[11]. These continued processes can lead, in aggregate, to increased pressure in the portal vein, *i.e.*, portal hypertension. The portal vein is normally approximately 8 cm in length and usually < 13 mm in diameter. It is formed by the union of the splenic and superior mesenteric vein systems; the inferior mesenteric vein enters one of these vessels, or at their junction, quite variably. Portal hypertension is defined as being 6 mmHg or greater as measured by the wedged hepatic vein gradient, and in particular, ascites formation usually occurs at 8 mmHg or greater. For completeness, it is noted that further clinical decompensation in the form variceal formation (10 mmHg), increased risk of variceal bleeding (12 mmHg) and risk for recurrent variceal bleeding (20 mmHg), correlate nicely with these increasing portal pressures[12-16]. This clinical sequence portends significant morbidity and mortality and can be interlaced with relatedfurther complications of hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), hepato-hydrothorax (HHT) and hepatorenal syndrome (HRS)[12].

Thus in the setting of portal hypertension, backflow and stasis of vasodilatory substances, *e.g.*, nitric oxide, begin to accumulate[17]. This causes, amongst other results splanchnic vasodilation with resultant hypoperfusion (although even when globally euvolemic or hypervolemic) of the renal system. Appropriately in this sense, thereninangiotensin-aldosterone system (RAAS) is activated leading to aggressive fluid retention[18-20]. In brief, renin is secreted from the renal juxtaglomerular apparatus (JGA) around the proximal nephrons in response to changes in vascular pressures, changes in serum sodium, and from activation of the sympathetic nervous system[17]. It in turn will convert angiotensinogen (made in the liver) to angiotensin I which is further converted to angiotensin Ⅱ by angiotensin converting enzyme (ACE) in the lungs[17-19]. Angiotensin Ⅱ has multiple important functions that drive fluid acquisition and retention, including stimulation of the thirst drive, release of aldosterone from the zona glomerulosa of the adrenal cortex, and secretion of vasopressin from the posterior pituitary[17-19]. This excess retained blood volume is thought to leak-out (filtered in a sense) directly from both the liver surface, and the mesenteric vessels. This latter mechanism is due to increased hydrostatics and vascular wall permeability, and concurrently decreased oncotic (osmotic) fluid retention in the form of absolute or relative hypoalbuminemia.

These three parameters, as described in the classical Starling equation, overwhelm the reabsorptive capacity of the peritoneal surface and lymphatic system[17-19].

Normally, the peritoneal cavity is decompressed and has a pressure of 5-10 mmHg, containing approximately 25-50 mL of serous fluid. This fluid normally provides a low resistance film over which bowel can move past each other and further hydrates the serosal surfaces maintaining pliability and integrity. The maximum absorption of fluid out of the peritoneum is approximately 850 mL/d in optimal settings. This property of absorption (selective filtration) provides the theory under which peritoneal dialysis operates[21,22]. It can be observed that alterations in the properties of the lymphatic system or the peritoneal surface area, either by inflammatory, infectious or fibrotic/mechanical processes can alter optimal re-absorption. Thus, continued dysregulation of these parameters can lead to profound ascitic fluid retention.

CLINICAL PRESENTATION

Ascites represents a very common manifestation of decompensated cirrhosis and thus on presentation[1,12] if cirrhosis has not already been defined for the patient, risk factors for its usual precursors, namely alcoholic use, viral hepatitis and NASH should be explored[1,12]. The clinical presentation of ascites is variable: it can occur slowly as observed in common and classical liver diseases, or suddenly as in new mechanical obstruction to the major vessels. For instance, hepatic or portal vein thrombosis, compression of the IVC due to trauma with a hematoma or infection, or acute hepatic failure. In the setting of thrombosis, causes for a hypercoaguable state should be sought: infectious, inflammatory, malignancy or hematologic genetic dispositions.Ascites can be painless, and if it is associated with abdominal pain may simply represent discomfort from mechanical distension, or super-imposed infection as in SBP, or even hepatocellular carcinoma[12,23]. Thus, while ascites represents a natural progression of cirrhosis, its appearance should prompt a careful investigation for other causes and complications as well[12].

An increase in abdominal girth can be due to a few generic processes. An increase in the width of the abdominal wall itself, *i.e.*, an enlarging panniculus; or it can represent the accumulation of solid, gas or liquid within the intestines or peritoneal space. Solid causes can represent retained and accumulating stool in constipation, or a malignant mass such ovarian cancer. Gaseous distension can also be observed in those with constipation or small intestinal bacterial overgrowth. Liquid retention, when focused, can represent a cystic object or loculated ascites. When the liquid is distributed uniformly, one certainly considers non-complicated ascites from liver or other sources (*vida supra*). The most common clinical complaints associated with liver related-ascites are an increase in abdominal girth, abdominal fullness, discomfort or ache, shortness of breath, early satiation and a sense of reduced mobility[12,22,24]. These symptoms are sensibly scaled to the actual amount of volume. Ascites can be of three severities: grade Ⅰ, wherein it is diagnosed by abdominal ultrasound, which requires approximately 100 mL of fluid within the peritoneum (recall that normal volume is approximately 25-50 mL); grade Ⅱ, implying at least 1000 mL of peritoneal fluid, which can be detected with physical examination through the classic exam findings of sagging flanks, shifting dullness, fluid-wave, and the more laborious and rarely utilized Puddle's sign;grade Ⅲ, manifested as a grossly distended abdomen, implying liters of ascitic fluid. This final grade can elicit a severe form of discomfort, and may be described as a tense ascites[1,12,22,24].

PARACENTESIS AND LABORATORY TESTING

Proper evaluation of ascites rests upon direct assessment through paracentesis: to characterize the fluid origin, and whether it is sterile, infectious and/or malignant. Unfortunately, there has been much lore related to the contra-indications and complications of this procedure. As with any procedure, coagulation status is a reasonable concern, and indeed in cirrhotics with ascites their coagulation status is altered but it is not at all obvious in which direction (pro- or anti-coagulant)[25]. Certainly there is a deficiency in the production and/or activity of coagulation compounds as would be indicated by the altered international normalized ratio (INR), but this parameter does not measure all coagulation factors, *e.g.*, protein C - a procoagulant. The idea that these patients are "auto-anticoagulated" is not true, and they can in fact be at real risk for thrombo-embolic disease[26]. Considering this problematic background, one must look at the empiric data, and although limited, suggests that paracentesis has been well-tolerated in patients with platelet counts below 20000 cells/mm^3 and an INR as high as 8.7[27-29]. Complications of wall hematoma requiring transfusion and infection are remote. A reasonable absolute contra-indication would be in disseminated intravascular coagulation[12]. The evidence for requisite transfusions of blood products, by non-hepatology procedural services, to meet the arbitrary limits of an INR < 1.5 or platelets > 50000 cells/mm^3 is unfounded, wasteful in resources and time, and itself incurs risks of transfusion reactions.

A diagnostic paracentesis, as opposed to a therapeutic paracentesis (*vida infra*), requires approximately 30-50 mL, and is mandatory in all cases of new onset ascites or ascites occurring in an individual with a change in clinical status to include fever, abdominal pain, new onset or worsening HE and any sign or symptom of infection generally. Paracentesis may be revealing for SBP even in hospital admissions not thought related to hepatic disease, *e.g.*, a presentation of weakness with painless ascites[24,28]. Ascitic fluid analysis in all cases should include cell counts and differential, albumin and total protein, and ascitic fluid culture aliquoted at the bedside[28]. Other studies depending upon the clinical situation or appearance of the ascitic fluid can include lactate dehydogenase

(LDH), cytology, amylase, glucose, total protein (TP), and triglycerides[12].

In regards gross appearance, ascitic fluid that is non-neutrocytic nor infected should be clear to yellow and transparent. In normal ascitic fluid the neutrophil count should be < 250 cells/mm^3, wherein the neutrophils are usually presented as a percentage of the total white blood cell (WBC) count. A common misinterpretation is to read this percentage as the absolute number of neutrophils, potentially missing a diagnosis of SBP. An elevated WBC count itself is certainly indicative of inflammation, and usually, but not definitively of infection, *e.g.*, SBP[12,28]. Other molecules such as lactoferrin have been evaluated for utility as sensitive ascitic biomarkers of infection but have yet to yield cost-effective results[30,31]. In the setting of peritoneal dialysis patients, lower thresholds for peritoneal infection have been described[32], *e.g.*, > 50 neutrophils/mm^3. In cases of "bloody taps", a correction factor of subtracting 1 neutrophil for every 250 red blood cells (RBCs) should be implemented when defining the type of ascites. If a milky appearance is observed it could suggest a high triglyceride count (chylous ascites from injured lymphatic ducts) of > 100-200 mg/dL[33]. An elevated ascitic fluid amylase level would be very suggestive for pancreatic ascites, *e.g.*, in the setting of a patient with chronic pancreatitis with pseudocysts, and a history of alcohol abuse.

A basic analysis of ascitic fluid albumin can be instructive when compared to serum albumin as the SAAG (where ≥ 1.1 g/dL defines a high albumin gradient) suggests portal-hypertension origin with 97% sensitivity[11]. Accuracy is decreased if the serum and ascitic fluid albumin are not drawn at the same time, or if the serum albumin is < 1.1 g/dL[12]. Note that one cannot infer that portal hypertension is from cirrhosis, although this may be a common cause, but other causes pre- and post-hepatic (*vida supra*) can also present in this fashion as well[12]. For instance cardiac ascites, a post-hepatic cause, with a SAAG ≥ 1.1 g/dL and an ascitic TP > 2.5 mg/dL, is a reasonable conclusion in the appropriate patient who has a history of heart failure, elevated brain natriuretic peptide, and a dilated IVC[34].

INFECTIOUS ASCITIC FLUID TREATMENT

The interface between the bowel, the intestinal microbiota, and the ascitic fluid is a dynamic one[35,36]. There is a constant translocation of bacteria across the bowel wall; the wall integrity is variable in part due to host genetics, nutritional status and local bacterial interactions. There is usually clearance of these invading bacteria by the immune system after surveillance and capture by neutrophils and macrophages with assisted opsonic molecules, *e.g.*, immunoglobulins or complement[37,38]. The generation of SBP thus likely is a manifestation of (1) bacterial type and burden; (2) gut integrity; (3) volume status; and (4) local and global immune function[37-39]. The symptoms of SBP can range from fevers and abdominal pain to a more subtle change in mental status, *e.g.*, HE, to being totally asymptomatic[12].

Infectious ascitic fluid is analyzed conceptually and practically through cell count/differential and fluid culture and is configured into four categories, the most important being SBP, defined as a neutrophil count > 250 cells/mm^3 and a positive mono-microbial ascitic culture[12,40]. If the cell count is < 250 cells/mm^3 and there is a positive ascitic culture this is defined as non-neutrocytic bacterascites (NNBA), whereas a negative ascitic culture with > 250 cells/mm^3 is culture-negative neutrocytic ascites (CNNA). A neutrophil count > 250 cells/mm^3 in the setting of a positive polymicrobial ascitic culture suggests, usually in the setting of bowel perforation, a secondary bacterial peritonitis. This diagnosis is supported by ascitic TP > 1 g/dL, glucose < 50 mg/dL and LDH > 225 U/L, the so-called Runyon's criteria[41]. In practice, with a positive neutrophil count, while culture results are pending, a provisional diagnosis of SBP will be granted and antimicrobial treatment initiated (*vida infra*). Given appropriate clinical indications NNBA and CNNA are treated in similar fashion to SBP. Secondary bowel peritonitis, beyond the utilization of antibiotics to include anaerobic coverage, will necessitate imaging and intervention for presumed bowel leak and/or perforation.

Standard treatment for SBP involves immediate implementation of third-generation cephalosporin such as *iv* ceftriaxone 1-2 g daily for five days, although oral fluoroquinolones have been utilized with success as well[42,43]. Repeat paracentesis is not needed unless there is clinical indication of failing treatment. Given the risks of renal dysfunction, specifically HRS (*vida infra*), in the setting of alterations in effective circulating volume, *iv* albumin has been utilized to maintain oncotic tone and renal perfusion. Initial studies demonstrated a benefit when *iv* albumin was dosed as 1.5 g/kg on day 1 and 1.0 g/kg on day 3, yielding renal protection and improved mortality[44]. Sub-analysis of these patients, further prompted by the large cost of *iv* albumin, suggested that patients with SBP and blood urea nitrogen (BUN) > 30 mg/dL and total bilirubin (TB) > 4 mg/mL would best benefit[45]. Ideally, one would seek for prevention of SBP as opposed to reactive treatment, and in this regard three groups have shown to benefit from antibiotic prophylaxis. In those (1) with prior SBP, oral norfloxacin 400 mg daily or equivalent indefinitely; (2) patients in the setting of gastrointestinal hemorrhage, to receive *iv* ceftriaxone 1 g daily × 7 d or equivalent; and (3) hospitalized patients with ascitic TP < 1.5 g/dL and serum Na < 130 mmol/L or BUN > 25 mg/dL or serum creatinine (Cr) > 1.2 mg/dL; otherwise TP < 1.5 g/dL with Child-Turcotte-Pugh (CTP) score > 9 and TB > 3 mg/dL, to receive oral ciprofloxacin 500 mg daily or oral trimethoprim-sulfamethoxazole double-strength daily[46-52].

NON-INFECTIOUS ASCITIC FLUID TREATMENT

Insofar as ascites represents a component of ongoing

cirrhotic decompensation, reversible behaviors contributing to the primary process, *e.g.*, alcoholic intake in a patient with alcoholic-induced cirrhosis, or diabetes and hyper-lipidemia in NASH patients, should be controlled[53]. Additionally, external therapy support groups and family involvement may prove crucial in helping the patient maintain sobriety and therapeutic compliance. A diet consisting of 2000 mg/d or less of salt (equivalent to 88 mmol/d of Na) is advocated given the physiologic limits of serum Na processing and secretion through the urine[53-56]. Serum Na governs volume status generally, and thus fluid restriction is not required and is likely not practical. Overloaded states with hyponatremia, even to levels between 110-120 mmol/L are common and well tolerated when approached slowly. Adherence to such a restricted Na diet can be evaluated by measuring 24-h urinary Na, wherein at least 78 mmol/d should be excreted (with water following Na) and resultant weight loss. More practically, a spot urine Na to potassium (K) ratio > 1 in the setting of weight gain also suggests dietary non-adherence[24]. Given the prognosis of ascites as common manifestation of decompensated cirrhosis, and the increased risk for mortality, these patients should be evaluated for OLT, the expedience of which is gauged approximately by their model for end-stage liver disease (MELD) score (*vida infra*)[1,6,12]. Although not absolute, a sobriety period, in the case of alcoholic cirrhosis, of approximately 6 mo is required of these patients as a predictor of compliance. Furthermore, certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors (ACEIs), and antibiotics such as aminoglycosides, should be avoided in patients with cirrhotic ascites. NSAIDs inhibit prostaglandins (which function to dilate afferent arterioles) whereas ACEIs inhibit ACEs (which activate angiotensin Ⅱ, which functions to constrict efferent arterioles). In either case regulation of glomerular perfusion is diminished, increasing potential for renal injury. Antibiotics such as aminoglycosides can be directly nephrotoxic.

Beyond dietary and behavioral measures, or those who cannot tolerate such restrictions, diuretic therapy provides another method for ascitic fluid control[57,58]. The standard combination includes spironolactone, an aldosterone antagonist, which down-regulates Na channels from the apical surface of the principal cells of the renal cortical collecting ducts; and, furosemide a Na-K-2 chloride (Cl) symport inhibitor in the ascending limb of the loop of Henle of the kidney. Spironolactone has a half-life of approximately 24 h, whereas furosemide has a half-life of approximately 1.5 h. They are utilized in a ratio of 100 mg of spironolactone to 40 mg of furosemide, which in theory provides for robust natriuresis with subsequent flow of water, while maintainingnormokalemia[24,56]. Spironolactone is initiated at 100 mg/d and increased every 5-7 d (in 100 mg steps) to a maximum of 400 mg/d, as needed for response. Furosemide is initiated at a dose of 40 mg/d to be increased at 40 mg/d until a maximum of 160 mg/d is achieved[24].

Patients should undergo frequent clinical and biochemical monitoring particularly during the first month of diuretic treatment. The maximum recommended weight loss during diuretic therapy for ascites should be 0.5 kg/d in patients without edema and 1 kg/d in patients with edema. These diuretics have proven to be an excellent method for slow fluid removal and commensurate weight loss. The goal of long-term treatment is to maintain the patient free of ascites with the lowest dose of diuretics. There are no absolute levels in regards to the degree of renal impairment or hyponatremia for which diuretics should not be initiated. However progressive renal injury with a Cr rise to > 1.5 mg/dL and hyponatremia < 120 mmol/L, respectively are sensible parameters which should elicit caution and tapering or cessation of diuretics. In patients with chronic kidney disease (CKD) or transient alterations in renal function, which are common in these patients, likely higher doses of diuretics will be required. The physician should be weary for diuretic-induced pre-renal acute kidney injury (AKI) or the HRS (*vida infra*). In this setting, there are likely to be frequent episodes for hyperkalemia given the usage of the spironolactone[24]. Additionally, intractable muscle cramps may develop, and thus precipitate a reduction of diuretics[58]. Alternative drugs to spironolactone, usually given the side-effects of gynecomastia and/or sexual dysfunction, or those allergic to the sulfa moiety, may be given amiloride. Amiloride is a direct inhibitor of the apical Na channel in the principal cells of the renal cortical collecting duct[59]. Furosemide can be exchanged for bumetanide, a similar acting diuretic, in those not responding to high doses. It is approximately × 40 more potent than furosemide with a similar side-effect profile[60,61].

More recently, a novel class of compounds has been generated to exploit the pathway of vasopressin[62]. Vasopressin is a naturally occurring compound built in the hypothalamus and stored in the posterior pituitary which is then secreted in response to alterations in blood volume and high serum osmolarity. In such settings it will bind the vasopressin-2 (V2) receptor on the basolateral surface of the principal cells of the renal cortical collecting ducts and through intra-cellular signaling promote the insertion of aquaporin 2 channels in the apical surface to allow for free water entry[62]. This process naturally concentrates urine while expanding total body volume.

In particular one compound, tolvaptan, has been approved for use in volume dysregulated states such as cirrhosis, congestive heart failure and syndrome of inappropriate anti-diuretic hormone[63]. By blocking vasopressin from binding the V2 receptor, a massive aquaresis takes place with correction of the volume state and normalization of serum Na concentration. In patients with a serum Na < 135 mmol/L, tolvaptan is dosed at 15 mg/d in an inpatient setting, and can be up-titrated by 15 mg/d to a maximum of 60 mg/d[63]. Significant improvement in serum Na concentration with tolvaptan, compared to placebo, was observed within 8 h of usage. Given the significant aquaresis, (1) patients should not be hypovolemic; (2)

they should have adequate thirst mechanism and access to fluids; and (3) should have their electrolytes monitored closely to prevent overly rapid correction, which in acute settings can lead to osmotic demyelination syndrome[64-66].

AUGMENTED MEDICAL MANAGEMENT OF ASCITES

While diuretics provide excellent maintenance of volume status in decompensated cirrhotics, rapid treatment for ascites, especially tense ascites (grade Ⅲ), is best through a therapeutic large-volume paracentesis (LVP)[12,24,67]. LVP can be performed all at once, wherein a catheter is temporarily placed and removed, or with an indwelling peritoneal drain for up to three days to slowly remove ascitic fluid over that time. Notably, the peritoneal drain method of LVP is not associated with increased frequency of SBP[68]. An initial LVP whether in an outpatient or inpatient setting, should be sent for ascitic fluid cell count/differential and cell culture to assess for SBP. Up to 15% of LVP may be associated with paracentesis induced circulatory dysfunction (PICD), which is characterized by an activation of the RAAS due to true or perceived volume dysregulation: (1) arterial underfilling and unloading of high-pressure baroreceptors; (2) stimulation of non-osmotic hypersecretion of vasopressin; (3) free water retention and dilutional hyponatremia; and (4) associated renal dysfunction[69]. Given these concerns, *iv* albumin replacement (8.5 g/kg for each liter of ascitic fluid removed) is indicated in cases where more than 5 L of ascitic fluid is removed[70-72]. Albumin, the most abundant circulating protein in the plasma, is endowed with an array of non-oncotic effects as well, including functioning as an anti-oxidant, anti-inflammatory and positive inotrope[73].

Despite such success, given the risks inherent in the use of *iv* albumin, as a blood product and its cost, other modalities have been attempted. Terlipressin, with a half-life of 6 h, is a vasopressin analog with selectivity for the V1 receptors on vascular smooth muscle cells, which induces vasoconstriction. In theory the maintenance of vascular tone through terlipressin should reduce, at least in part, some factors that generate PICD[74]. A notable study suggested that in cirrhotic patients with tense ascites who were assigned to receive standard *iv* albumin replacement or terlipressin (total 3 mg *iv*) after therapeutic paracentesis, both were effective in reducing manifestations of PICD. There were no significant differences in arterial blood volume (as measured by plasma renin and aldosterone levels) nor in renal impairment or hyponatremia between either group[75].

Following the LVP, patients should receive the minimum dose of diuretics necessary to prevent re-accumulation of the ascites. A small population of ascites patients may be defined as having refractory ascites: ascites which cannot be adequately controlled through dietary, pharmacologic or LVP modalities[74]. Furthermore, a subgroup of patients maybe intolerant to augmented medical management given symptomatic or biochemical side-effects, and thus classified as diuretic-intractable ascites[74,76,77]. Or, a sub-group of patients may retain significant ascites despite optimized and maximal therapy and thus are classified as diuretic-resistant ascites. These groups of patients may require serial LVP, in some cases up to twice per month, which can be time-consuming, costly and increase the risk for iatrogenic infections. There have been smaller studies examining the role of other pharmacologic modalities in refractory ascites, such as midodrine, an alpha-1 agonist upon arterial and venous vessels, inducing increased vascular tone. Midodrine has been shown to be as effective as *iv* albumin in preventing PICD in such patients with refractory ascites, with minimal side-effects and high cost-efficiency[78]. Compare this to terlipressin, which showed similar outcomes in such patients (*vida supra*)[75]. Note however that in the latter case, terlipressin must be given through intravenous, and it is currently not available in the United States. Interestingly, non-selective beta-blockers, which have shown benefit in cirrhotic patients in preventing variceal hemorrhage, are associated with increased mortality, 4 × higher compared to those not on beta-blockers, when observed specifically in those patients with refractory ascites[79]. It is postulated that these beta-blockers may be inhibiting compensatory cardiac output (*via* a negative inotropic effect) and thus pre-disposing to PICD. Further is the interesting finding that in these patients the CTP score, which includes an ascites parameter, is better at predicting mortality than the MELD score. These results require further validation, but may indicate that in the fraction of patients with refractory ascites, beta-blockers should be contra-indicated.

The prognosis of patients with refractory ascites is very poor, and if eligible, should be referred for OLT and/or transjugular intra-hepatic portosystemic shunt (TIPS) as bridge to OLT[80-85]. TIPS is a procedure that has been evolving since the 1980s[86] and relies on the principle of establishing direct continuity (low-resistance) from a large portal branch to a hepatic vein by way of a shunting stent. This stent bypasses the cirrhotic (high-resistance) parenchymal tissue which had generated the portal hypertension and resultant ascites[83]. Recall the portal hypertension develops in the setting of a HWPG of 6 mmHg or greater, and that at 8 mmHg ascites develops, and at 10-12 mmHg varices develop with increased risk of hemorrhage. TIPS is a quite common procedure and not technically demanding with current radiologic techniques. Procedural complications such as failed TIPS deployment and endotipsitis are rare. Concern for TIPS stent thrombosis post-procedurally is minimal in the era of covered stents[83,87,88]. Its strongest indications are in those with refractory ascites and/or recurrent variceal hemorrhage[83]. Overall TIPS has shown benefit in the decreased requirement for diuretics, improved quality of life, and likely a trend towards improved mortality when compared to repetitive paracentesis in patients with refractory ascites[82-85,87-92]. In the MELD era, a score of 14 or less suggests a good candidate for TIPS procedure, a score of 24 or greater, suggests that OLT is more benefi-

cial, and a score in-between requires individual consideration of a risk/benefit analysis to the patient[83,93].

Whether TIPS is ultimately cost-effective, in which most of the cost is up-front at the time of procedure, compared to LVP, where cost is aggregated over time, is still an open question and likely institution dependant. Total TIPS cost have gone down given the decreased requirement for revision in the era of covered stents. Given the physiologic mechanism by which TIPS operates, certain concerns naturally arise: TIPS is contra-indicated in patients with (1) significant right heart failure or pulmonary hypertension as it will place rapid unduevolume burden upon these organs; (2) patients with recurrent HE, as it will not allow for as much detoxification and regulation of the culprit amines; (3) polycystic liver disease or a liver containing malignancy or abscess; (4) active infection; and (5) severe renal disease, given rapid alterations in vascular volume distribution[83,94,95].

There is a small group of patients with refractory ascites, who for a variety of reasons cannot undergo TIPS or OLT, and for whom serial paracentesis has resulted in too much distress or protein losses. In many cases these represent patients who also have peritoneal malignant implants[96-99]. For these scenarios, a peritoneal-venous shunt (PVS) was envisioned, conserving and directing fluid and protein from the peritoneum into the superior vena cava (SVC). There are two types, the LaVeen and the Denver, both one-way valve stents, which empty into the SVC based upon different opening pressures[96]. Contra-indications include loculated ascites, coagulation disorders, and advanced cardiac or renal failure; hemorrhagic ascites and high ascetic TP can cause drain occlusion. Interestingly, in malignant ascites, limited studies have not demonstrated increased systemic metastasis facilitated by stent transfer into the circulatory system. Overall these shunts have not prolonged survival in these patient populations, nor those with HRS[97]. Shunt patency is poor, with < 20% at 2 years. Furthermore SBP and/or sepsis require PVS removal[97]. In general, PVS should be considered as sub-optimal therapy, after standard therapies of diuretics, LVP and TIPS have failed or are contra-indicated[12,83,97].

PULMONARY COMPLICATIONS

HHT is an accumulation of ascitic fluid within the pleural space that occurs in approximately 10% of cirrhotics. In about 85% of these patients it is right-sided, and in others it can be bilateral or even left-sided alone[100]. The etiology is thought to be from the combination of both hemostatic pressure from the ascites pushing through diaphragmatic defects or rents in combination with the "pull" of the negative intra-thoracic pressure[101]. In some cases this combination can effectively drain the peritoneal cavity such that one may have HHT in the absence of a distended abdomen. Normally the pleural space is a potential one, wherein pleural fluid volume is approximately < 25 mL per lung, providing a low frictional interface between the parietal and visceral pleurae. The normal pleural fluid is generated from the parietal pleura, and to a lesser extent the visceral pleura, and reabsorbed by pleural lymphatics. In the setting chronic disease, lymphatic absorption can increase to > 20 × normal baseline rates[102].

Cirrhotic patients who develop a significant amount HHT (approximately after 1 L) tend to have symptoms of shortness of breath and cough. The accumulation of this fluid can lead to hypoexemia, atelectasis, pneumonia and empyema[99,101]. Initial evaluation can include a lateral and posteroanterior chest X-ray, which will show blunting at approximately 50 and 200 mL, respectively. A CT scan of the chest can also be considered to assess for other causes of these symptoms and signs. Initial management should involve a thoracentesis for both diagnostic and therapeutic purposes[99,101]. Similar to a paracentesis, the most useful testing will be to examine the fluid for cell count/differential, cell culture, albumin and TP, with results that should be similar to classical pleural effusions defined as a transudate rather than exudate by Light's criteria[103]. Infected pleural fluid, *i.e.*, spontaneous bacterial empyema (SBE), should always be of concern, and it has been identified in cases where the ascites did not have SBP and in even cases without any ascites[104]. SBE is diagnosed by a positive culture (usually *Escheria*, *Streptococcus* or *Enterococcus*) or a neutrophil count of > 250 cell/mm^3. Standard treatment includes a third-generation cephalosporin or equivalent antibiotic[104]. Chest tubes should not be attempted given the high risk of procedural complications, *e.g.*, abdominal penetration, bleeding, and infection. There is also justified concern for the chronic loss of pleural fluid protein and serum electrolyte abnormalities[105].

Beyond the initial evaluation with thoracentesis, standard measures of dietary restriction and diuretic therapy should be continued[83]. In cases of persistent HHT that have failed these therapies, TIPS has been attempted under the same principles for treatment of refractory ascites in select patients[106,107]. Another procedure is pleurodesis, a process in which an agent such as tetracycline or talc are introduced into the pleural space after which a robust inflammatory reaction occurs that results in visceral to parietal pleural wall fusion[108]. Unfortunately, in most cirrhotic patients, the flow of ascitic fluid entry across the diaphragm and into the pleural space is so high that there is rarely enough time for the pleurae to maintain good approximation for durable fusion. It should only be considered in those patients who have failed first line therapies, and are ineligible for TIPS or OLT[83].

RENAL COMPLICATIONS

Renal injury, encompassing a spectrum from acute to chronic causes, is very common in decompensated cirrhotic patients given the significant alterations in volume and hormonal regulation, vascular tone, immune function and related infections, and the utilization of numerous medications and contrast-assisted procedures[109-111]. Classically AKI is segregated into pre-renal, renal and post-renal causes, and with severe or sustained insult

this can lead CKD with the possible utilization of renal replacement therapy (RRT) in either case. For instance, pre-renal causes might include hypovolemia or renal artery thrombosis; renal (intrinsic) causes might include toxicity from infection, malignancy or medications and *iv* contrast; post-renal causes might include ureteral stone obstruction or extrinsic ureteral compression by a pelvic malignancy[109,111-114].

The HRS should be considered in all cirrhotic patients who develop pure AKI or AKI within a CKD setting[111,115]. HRS, as with any AKI, should be considered when a rise in serum Cr × 1.5 baseline and decrease in urine output are observed in the setting of cirrhosis, and confounding causes for pre-renal, renal and post-renal mechanisms have been reasonably excluded[109,115]. HRS occurs in approximately 30% of patients with SBP treated with antibiotics and is associated with a poor survival[12]. The exact etiology of HRS is unknown, but does involve (1) RAAS dysregulation with avid fluid retention (*vida supra*); (2) splanchnic vessel dilation and a local vasoconstrictive effect at the level of the nephron driven by renin, angiotensin Ⅱ and other vasoconstrictors; and (3) altered cardiac function[115]. The renal JGA continually perceives an effectively low circulating volume and thus continuously activates these volume retaining and vasoconstrive mechanisms.

The HRS is classified into two distinct subtypes: type 1 HRS is characterized by a rapid and progressive impairment in renal function (increase in serum Cr to ⩾ 2.5 mg/dL or a reduction in the Cr clearance (CrCl) to < 20 mL/min in less than two weeks; type 2 HRS is characterized by a slowly progressive impairment of renal function manifested by an increase in serum Cr to ⩾ 1.5 mg/dL or a CrCl to < 40 mL/min[111,115]. Survival in these patients is rather poor, with 50% mortality at less than one month for type 1 HRS and 50% mortality at 6 mo for type 2 HRS[74,116]. Given the complex intrinsic nature of the HRS, it is not surprising that it is defined by negation, *i.e.*, by that which it is not. The criteria for HRS have been evolving and currently include following criteria: (1) rise in serum Cr to > 1.5 mg/dL; (2) the absence of hypovolemic shock (defined by the withdrawl of diuretics and the failure of serum Cr to fall below 1.5 mg/dL in the setting of at least 1 L of saline or standard albumin fluid bolus); (3) the absence of nephrotoxic medications or recent *iv* contrast; and (4) the absence of intrinsic renal disease as assessed by renal ultrasound and proteinuria < 0.5 g/d and microhematuria < 50 RBCs/high powered field[12,74,111,115,116]. Note that sepsis is not part of the exclusion criteria; HRS is commonly precipitated by SBP in many instances, hence the rationale of antibiotic treatments (*vida supra*).

As the diagnosis of HRS can herald significant morbidity and mortality in cirrhotic patients OLT should be considered as definitive therapy, if they are eligible. Diuretics should be discontinued, and high grade ascites should be reduced with paracentesis as large peritoneal pressures can compress renal arteries (abdominal compartment syndrome), further worsening the renal insult[74]. Meanwhile, medical therapies may be considered as a temporizing measure, and work towards maintaining effective arterial perfusion of the kidneys. Terlipressin, an analog of vasopressin, has been much researched in the HRS, either in comparison to placebo, or in combination with *iv* albumin versus placebo, or in comparison to noradrenaline (norepinephrine), a classical vasoactive alpha adrenergic agonist[116-119]. Studies have supported the benefit of terlipressin in reversing HRS when given for at least 14 d, and which typically yield low relapse rates[116,117]. Further, although more limited, there has been data demonstrating reversal of HRS with noradrenaline similar to terlipressin[119]. Notably, in a few studies when terlipressin was administered with *iv* albumin there was reversal of HRS and improvement in mortality[120], although its value in septic patients is unknown. Terlipressin is usually dosed at 1 mg/6 h, and can be increased to 2 mg/6 h if no improvement in serum Cr is observed.

Similarly, midodrine, a vasoactive alpha adrenergic agonist with a half-life of approximately 4 h, has also demonstrated HRS benefit, and can be dosed at 10 mg three times per day (*tid*) and increased to 15 mg *tid*. Complementarily, octreotide (an inhibitor of splanchnic vasodilators, with a half-life of 1.7 h) is dosed at 100 mcg subcutaneously tid and up to 200 mg *tid* can be utilized. A therapeutic cocktail of these vasoactive agents, *e.g.*, midodrine or terlipressin, and octreotide, with the utilization of *iv* albumin dosed at up to 40 g per day in divided doses have demonstrated benefit in HRS[121-124]. It is preferable to use highly concentrated albumin, *e.g.*, 25% *vs* 5% albumin, given the reduced volume of solution and decreased third-spacing burden upon the patient. Successful treatment will manifest as a decrease in serum Cr, ideally by at least 1 mg/dL and an increase in urine output. If the serum Cr decreases to ⩽ 1.5 mg/dL, diuretics can be restarted at half the prior dosing with subsequent careful monitoring of volume status and serum Cr. Certainly, as with other forms of AKI, these patients should be carefully monitored: vital signs, mental status, urine output, electrolyte abnormalities, and overall for uremic signs, which would require emergent use of RRT such as hemodialysis[125].

Serum Cr is utilized as a practical, albeit imperfect marker, for renal function in the clinical setting. By extension, renal function has itself become a proxy for systemic health, and the importance of this fact is reflected in the integration of the serum Cr into the MELD score[126,127]. The MELD score is comprised of the serum TB, serum Cr and INR, yielding an integer score from 6 to 40 which predicts 90-d mortality in non-transplanted cirrhotic patients[128]. The MELD score has been more successful than prior risk stratification methods in prognosticating mortality and equitably distributing organs for appropriately eligible patients[129-131]. However, in its elegant simplicity, it unsurprisingly does not capture the total biology of cirrhosis. Thus certain modifications have been appended, in the form of exception points, notably to those who are on RRT or with low-staged hepatocellular carcinoma, amongst others[132].

As stated, OLT represents the definitive therapy for HRS types 1 and 2, and that while it may "cure" the HRS, it will still leave behind the residual CKD in many patients. Furthermore, as a result of the surgery itself (with significant volume shifts), and afterwards by the lifetime use of potentially nephrotoxic immunosuppressants and baseline co-morbidities, renal function can be expected to decline further, even necessitating RRT in some instances. Such consequences themselves herald significant morbidity and mortality for these transplanted patients. Given these concerns, simultaneous liver-kidney transplant (SLKT) has become prevalent in the MELD era with the following facts noted: (1) inconsistent eligibility criteria for SLKT that varies by transplant center; (2) there has not been consistent benefit to morbidity and mortality for these patients, as had been hoped; and (3) eligible kidneys are removed out of the pool for solitary kidney transplant recipients[132,133]. These problems represent an area of active research, with more formal guidance in development[133].

CONCLUSION

Ascites is a pathologic accumulation of fluid within the peritoneal cavity that is most commonly found incirrhotic patients, and its presence heralds significant morbidity and mortality[1,6,10]. The generation of cirrhotic ascites is multi-factorial, but is found in the setting of portal hypertension, and in essence is driven by global abnormalities in hormonal/cytokine regulation and effective vascular status, in a feed-forward cycle[17-19]. Ascites is problematic on many levels: directly, by causing symptoms of abdominal discomfort and early satiation[12]; and indirectly, by facilitating significant complications of infections and multi-organ dysfunction such as SBP, HHT and HRS[12,38,41,99,115]. The identification of ascites, once suspected, is easily determined through physical exam and imaging[23]. Diagnostic paracentesis is an integral procedure in determining the etiology of ascites and further delineating any associated infection or malignancy[24,28]. Ascites can be managed successfully by aggressive salt restriction and utilization of a diuretic regimen in most patients, however in some instances LVP or even TIPS may be required[54,56,67,83]. Given the complexity and prognosis associated with ascites, a multi-disciplinary approach is required, with work-up for OLT initiated in eligible patients[133]. The biomedical advances in understanding and treating ascites and its complications have been impressive, but nevertheless much work remains in optimizing patient care and patient outcomes.

REFERENCES

1 **Ginés P**, Quintero E, Arroyo V, Terés J, Bruguera M, Rimola A, Caballería J, Rodés J, Rozman C. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987; **7**: 122-128 [PMID: 3804191 DOI: 10.1002/hep.1840070124]

2 **Guevara M**, Cárdenas A, Uriz J, Ginès P. Prognosis in patients with cirrhosis and ascites. In: Ginès P, Arroyo V, Rodés J, Schrier RW, editors. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis and treatment. Malden: Blackwell, 2005: 260–270 [DOI: 10.1002/9780470987476.ch21]

3 **Ripoll C**, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS, Bosch J. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; **133**: 481-488 [PMID: 17681169 DOI: 10.1053/j.gastro.2007.05.024]

4 **Papyrus E**, Bryan CP. The *Papyrus* Ebers. New York: D Appleton and Company, 1931

5 **Planas R**, Montoliu S, Ballesté B, Rivera M, Miquel M, Masnou H, Galeras JA, Giménez MD, Santos J, Cirera I, Morillas RM, Coll S, Solà R. Natural history of patients hospitalized for management of cirrhotic ascites. *Clin Gastroenterol Hepatol* 2006; **4**: 1385-1394 [PMID: 17081806 DOI: 10.1016/j.cgh.2006.08.007]

6 **Heuman DM**, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004; **40**: 802-810 [PMID: 15382176 DOI: 10.1002/hep.1840400409]

7 **Arroyo V**, Rodés J, Gutiérrez-Lizárraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. *Am J Dig Dis* 1976; **21**: 249-256 [PMID: 1266841 DOI: 10.1007/BF01095898]

8 **Becker G**, Galandi D, Blum HE. Malignant ascites: systematic review and guideline for treatment. *Eur J Cancer* 2006; **42**: 589-597 [PMID: 16434188 DOI: 10.1016/j.ejca.2005.11.018]

9 **Seike M**, Maetani I, Sakai Y. Treatment of malignant ascites in patients with advanced cancer: peritoneovenous shunt versus paracentesis. *J Gastroenterol Hepatol* 2007; **22**: 2161-2166 [PMID: 18031375 DOI: 10.1111/j.1440-1746.2006.04793.x]

10 **Runyon BA**, Hoefs JC, Morgan TR. Ascitic fluid analysis in malignancy-related ascites. *Hepatology* 1988; **8**: 1104-1109 [PMID: 3417231]

11 **Runyon BA**, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* 1992; **117**: 215-220 [PMID: 1616215]

12 **Runyon BA**. Ascites and spontaneous bacterial peritonitis. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th ed. Philadelphia, PA: Saunders, 2010 [DOI: 10.1016/B978-1-4160-6189-2.00091-3]

13 **Lebrec D**, De Fleury P, Rueff B, Nahum H, Benhamou JP. Portal hypertension, size of esophageal varices, and risk of gastrointestinal bleeding in alcoholic cirrhosis. *Gastroenterology* 1980; **79**: 1139-1144 [PMID: 6969201]

14 **Pagliaro L**, D'Amico G, Pasta L, Politi F, Vizzini G, Traina M, et al. Portal hypertension in cirrhosis: Natural history. In: Bosch J, Groszmann RJ. Portal Hypertension. Pathophysiology and Treatment. Oxford, UK: Blackwell Scientific, 1994: 72-92

15 **Moitinho E**, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999; **117**: 626-631 [PMID: 10464138 DOI: 10.1016/S0016-5085(99)70455-5]

16 **Monescillo A**, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, Marrero JM, Buceta E, Sánchez J, Castellot A, Peñate M, Cruz A, Peña E. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology* 2004; **40**: 793-801 [PMID: 15382120 DOI: 10.1002/hep.1840400408]

17 **Teirstein AS**, Judson MA, Baughman RP, Rossman MD, Yeager H, Moller DR. The spectrum of biopsy sites for the diagnosis of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; **22**:

139-146 [PMID: 16053030 DOI: 10.1002/9780470987476.ch11]
18 **Schrier RW**, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; **8**: 1151-1157 [PMID: 2971015 DOI: 10.1002/hep.1840080532]
19 **Henriksen JH**, Møller S. Alterations of hepatic and splanchnic microvascular exchange in cirrhosis: local factors in the formation of ascites. In: Ginès P, Arroyo V, Rodés J, Schrier RW, editors. Ascites and renal dysfunction in liver disease. Malden: Blackwell, 2005: 174–185 [DOI: 10.1002/9780470987476.ch14]
20 **Llach J**, Ginès P, Arroyo V, Rimola A, Titó L, Badalamenti S, Jiménez W, Gaya J, Rivera F, Rodés J. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology* 1988; **94**: 482-487 [PMID: 3335320]
21 **Selgas R**, Bajo MA, Jimenez C, Sanchez C, Del Peso G, Cacho G, Diaz C, Fernandez-Reyes MJ, De Alvaro F. Peritoneal dialysis in liver disorders. *Perit Dial Int* 1996; **16** Suppl 1: S215-S219 [PMID: 8728196]
22 **Marcus RG**, Messana J, Swartz R. Peritoneal dialysis in end-stage renal disease patients with preexisting chronic liver disease and ascites. *Am J Med* 1992; **93**: 35-40 [PMID: 1626571 DOI: 10.1016/0002-9343(92)90677-4]
23 **Cattau EL**, Benjamin SB, Knuff TE, Castell DO. The accuracy of the physical examination in the diagnosis of suspected ascites. *JAMA* 1982; **247**: 1164-1166 [PMID: 7057606 DOI: 10.1001/jama.1982.03320330060027]
24 **Runyon BA**. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009; **49**: 2087-2107 [PMID: 19475696 DOI: 10.1002/hep.22853]
25 **Tripodi A**, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011; **365**: 147-156 [PMID: 21751907]
26 **Runyon BA**. Paracentesis of ascitic fluid. A safe procedure. *Arch Intern Med* 1986; **146**: 2259-2261 [PMID: 2946271 DOI: 10.1001/archinte.1986.00360230201029]
27 **Mannucci PM**. Abnormal hemostasis tests and bleeding in chronic liver disease: are they related? No. *J Thromb Haemost* 2006; **4**: 721-723 [PMID: 16634735 DOI: 10.1111/j.1538-7836.2006.01886.x]
28 **Grabau CM**, Crago SF, Hoff LK, Simon JA, Melton CA, Ott BJ, Kamath PS. Performance standards for therapeutic abdominal paracentesis. *Hepatology* 2004; **40**: 484-488 [PMID: 15368454 DOI: 10.1002/hep.20317]
29 **Pache I**, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. *Aliment Pharmacol Ther* 2005; **21**: 525-529 [PMID: 15740535 DOI: 10.1111/j.1365-2036.2005.02387.x]
30 **Parsi MA**, Saadeh SN, Zein NN, Davis GL, Lopez R, Boone J, Lepe MR, Guo L, Ashfaq M, Klintmalm G, McCullough AJ. Ascitic fluid lactoferrin for diagnosis of spontaneous bacterial peritonitis. *Gastroenterology* 2008; **135**: 803-807 [PMID: 18590731 DOI: 10.1053/j.gastro.2008.05.045]
31 **Kallwitz ER**. Ascites fluid lactoferrin: data emerges for a logical biomarker. *Gastroenterology* 2008; **135**: 731-733 [PMID: 18692054 DOI: 10.1053/j.gastro.2008.07.037]
32 **Piraino B**, Bailie GR, Bernardini J, Boeschoten E, Gupta A, Holmes C, Kuijper EJ, Li PK, Lye WC, Mujais S, Paterson DL, Fontan MP, Ramos A, Schaefer F, Uttley L. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 2005; **25**: 107-131 [PMID: 15796137]
33 **Cárdenas A**, Chopra S. Chylous ascites. *Am J Gastroenterol* 2002; **97**: 1896-1900 [PMID: 12190151 DOI: 10.1111/j.1572-0241.2002.05911.x]
34 **Runyon BA**. Cardiac ascites: a characterization. *J Clin Gastroenterol* 1988; **10**: 410-412 [PMID: 3418089 DOI: 10.1097/00004836-198808000-00013]
35 **Garcia-Tsao G**, Lee FY, Barden GE, Cartun R, West AB. Bacterial translocation to mesenteric lymph nodes is increased in cirrhotic rats with ascites. *Gastroenterology* 1995; **108**: 1835-1841 [PMID: 7768390 DOI: 10.1016/0016-5085(95)90147-7]
36 **Woodcock NP**, Robertson J, Morgan DR, Gregg KL, Mitchell CJ, MacFie J. Bacterial translocation and immunohistochemical measurement of gut immune function. *J Clin Pathol* 2001; **54**: 619-623 [PMID: 11477118 DOI: 10.1136/jcp.54.8.619]
37 **Garcia-Tsao G**, Albillos A, Barden GE, West AB. Bacterial translocation in acute and chronic portal hypertension. *Hepatology* 1993; **17**: 1081-1085 [PMID: 8514258 DOI: 10.1002/hep.1840170622]
38 **Ramachandran A**, Balasubramanian KA. Intestinal dysfunction in liver cirrhosis: Its role in spontaneous bacterial peritonitis. *J Gastroenterol Hepatol* 2001; **16**: 607-612 [PMID: 11422611]
39 **Pardo A**, Bartolí R, Lorenzo-Zúñiga V, Planas R, Viñado B, Riba J, Cabré E, Santos J, Luque T, Ausina V, Gassull MA. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. *Hepatology* 2000; **31**: 858-863 [PMID: 10733540 DOI: 10.1053/he.2000.5746]
40 **Runyon BA**, Hoefs JC. Culture-negative neutrocytic ascites: a variant of spontaneous bacterial peritonitis. *Hepatology* 1984; **4**: 1209-1211 [PMID: 6500513 DOI: 10.1002/hep.1840040619]
41 **Akriviadis EA**, Runyon BA. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. *Gastroenterology* 1990; **98**: 127-133 [PMID: 2293571]
42 **Navasa M**, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A, Marco F, Guarner C, Forné M, Planas R, Bañares R, Castells L, Jimenez De Anta MT, Arroyo V, Rodés J. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology* 1996; **111**: 1011-1017 [PMID: 8831596 DOI: 10.1016/S0016-5085(96)70069-0]
43 **Felisart J**, Rimola A, Arroyo V, Perez-Ayuso RM, Quintero E, Gines P, Rodes J. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology* 1985; **5**: 457-462 [PMID: 3888810 DOI: 10.1002/hep.1840050319]
44 **Sort P**, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]
45 **Poca M**, Concepción M, Casas M, Alvarez-Urturi C, Gordillo J, Hernández-Gea V, Román E, Guarner-Argente C, Gich I, Soriano G, Guarner C. Role of albumin treatment in patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2012; **10**: 309-315 [PMID: 22094025 DOI: 10.1016/j.cgh.2011.11.012]
46 **Rimola A**, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000; **32**: 142-153 [PMID: 10673079 DOI: 10.1016/S0168-8278(00)80201-9]
47 **Bernard B**, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. *Gastroenterology* 1995; **108**: 1828-1834 [PMID: 7768389 DOI: 10.1016/0016-5085(95)90146-9]
48 **Bernard B**, Grangé JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999; **29**: 1655-1661 [PMID: 10347104 DOI: 10.1002/hep.510290608]
49 **Fernández J**, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V, Such J, Ginès P, Arroyo V. Primary prophylaxis of spontane-

ous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007; **133**: 818-824 [PMID: 17854593 DOI: 10.1053/j.gastro.2007.06.065]
50 **Terg R**, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, Landeira C, Romero G, Dominguez N, Muñoz A, Levi D, Miguez C, Abecasis R. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. *J Hepatol* 2008; **48**: 774-779 [PMID: 18316137 DOI: 10.1016/j.jhep.2008.01.024]
51 **Ginés P**, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forné M, Miranda ML, Llach J, Salmerón JM. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990; **12**: 716-724 [PMID: 2210673 DOI: 10.1002/hep.1840120416]
52 **Singh N**, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann Intern Med* 1995; **122**: 595-598 [PMID: 7887554]
53 **Said A**, Williams J, Holden J, Remington P, Musat A, Lucey MR. The prevalence of alcohol-induced liver disease and hepatitis C and their interaction in a tertiary care setting. *Clin Gastroenterol Hepatol* 2004; **2**: 928-934 [PMID: 15476157 DOI: 10.1016/S1542-3565(04)00393-3]
54 **Bernardi M**, Laffi G, Salvagnini M, Azzena G, Bonato S, Marra F, Trevisani F, Gasbarrini G, Naccarato R, Gentilini P. 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 [PMID: 8336527 DOI: 10.1111/j.1600-0676.1993.tb00624.x]
55 **Ellison DH**. Diuretic drugs and the treatment of edema: from clinic to bench and back again. *Am J Kidney Dis* 1994; **23**: 623-643 [PMID: 8172204]
56 **Santos J**, Planas R, Pardo A, Durández R, Cabré E, Morillas RM, Granada ML, Jiménez JA, Quintero E, Gassull MA. Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety. *J Hepatol* 2003; **39**: 187-192 [PMID: 12873814 DOI: 10.1016/S0168-8278(03)00188-0]
57 **Fogel MR**, Sawhney VK, Neal EA, Miller RG, Knauer CM, Gregory PB. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. *J Clin Gastroenterol* 1981; **3** Suppl 1: 73-80 [PMID: 7035545 DOI: 10.1097/00004836-198100031-00016]
58 **Angeli P**, Albino G, Carraro P, Dalla Pria M, Merkel C, Caregaro L, De Bei E, Bortoluzzi A, Plebani M, Gatta A. Cirrhosis and muscle cramps: evidence of a causal relationship. *Hepatology* 1996; **23**: 264-273 [PMID: 8591851 DOI: 10.1002/hep.510230211]
59 **Angeli P**, Dalla Pria M, De Bei E, Albino G, Caregaro L, Merkel C, Ceolotto G, Gatta A. Randomized clinical study of the efficacy of amiloride and potassium canrenoate in nonazotemic cirrhotic patients with ascites. *Hepatology* 1994; **19**: 72-79 [PMID: 8276370 DOI: 10.1002/hep.1840190113]
60 **Flamenbaum W**, Friedman R. Pharmacology, therapeutic efficacy, and adverse effects of bumetanide, a new "loop" diuretic. *Pharmacotherapy* 1982; **2**: 213-222 [PMID: 6763204]
61 **Voelker JR**, Cartwright-Brown D, Anderson S, Leinfelder J, Sica DA, Kokko JP, Brater DC. Comparison of loop diuretics in patients with chronic renal insufficiency. *Kidney Int* 1987; **32**: 572-578 [PMID: 3430953 DOI: 10.1038/ki.1987.246]
62 **Greenberg A**, Verbalis JG. Vasopressin receptor antagonists. *Kidney Int* 2006; **69**: 2124-2130 [PMID: 16672911 DOI: 10.1038/sj.ki.5000432]
63 **Schrier RW**, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006; **355**: 2099-2112 [PMID: 17105757 DOI: 10.1056/NEJMoa065181]
64 **Gerbes AL**, Gülberg V, Ginès P, Decaux G, Gross P, Gandjini H, Djian J. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. *Gastroenterology* 2003; **124**: 933-939 [PMID: 12671890 DOI: 10.1053/gast.2003.50143]
65 **Wong F**, Gines P, Watson H, Horsmans Y, Angeli P, Gow P, Minini P, Bernardi M. Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. *J Hepatol* 2010; **53**: 283-290 [PMID: 20541828 DOI: 10.1016/j.jhep.2010.02.036]
66 **Ginès P**, Wong F, Watson H, Terg R, Bruha R, Zarski JP, Dudley F. Clinical trial: short-term effects of combination of satavaptan, a selective vasopressin V2 receptor antagonist, and diuretics on ascites in patients with cirrhosis without hyponatraemia--a randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2010; **31**: 834-845 [PMID: 20102356]
67 **Ginés P**, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, Rimola A, Viver J, Camps J, Jiménez W. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. *Gastroenterology* 1987; **93**: 234-241 [PMID: 3297907]
68 **Van Thiel DH**, Moore CM, Garcia M, George M, Nadir A. Continuous peritoneal drainage of large-volume ascites. *Dig Dis Sci* 2011; **56**: 2723-2727 [PMID: 21735084 DOI: 10.1007/s10620-011-1792-x]
69 **Ruiz-del-Arbol L**, Monescillo A, Jimenéz W, Garcia-Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology* 1997; **113**: 579-586 [PMID: 9247479 DOI: 10.1053/gast.1997.v113.pm9247479]
70 **Ginès P**, Tító L, Arroyo V, Planas R, Panés J, Viver J, Torres M, Humbert P, Rimola A, Llach J. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988; **94**: 1493-1502 [PMID: 3360270]
71 **McCormick PA**, Mistry P, Kaye G, Burroughs AK, McIntyre N. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. *Gut* 1990; **31**: 204-207 [PMID: 2311979 DOI: 10.1136/gut.31.2.204]
72 **Garcia-Martinez R**, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: Pathophysiologic basis of its role in the treatment of cirrhosis and its complications. *Hepatology* 2013 Feb 19; Epub ahead of print [PMID: 23423799 DOI: 10.1002/hep.26338]
73 **Bortoluzzi A**, Ceolotto G, Gola E, Sticca A, Bova S, Morando F, Piano S, Fasolato S, Rosi S, Gatta A, Angeli P. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. *Hepatology* 2013; **57**: 266-276 [PMID: 22911662 DOI: 10.1002/hep.26021]
74 **European Association for the Study of the Liver**. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]
75 **Singh V**, Kumar R, Nain CK, Singh B, Sharma AK. Terlipressin versus albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized study. *J Gastroenterol Hepatol* 2006; **21**: 303-307 [PMID: 16460491]
76 **Arroyo V**, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996; **23**: 164-176 [PMID: 8550036 DOI: 10.1002/hep.510230122]
77 **Sanyal AJ**, Genning C, Reddy KR, Wong F, Kowdley KV, Benner K, McCashland T. The North American Study for the Treatment of Refractory Ascites. *Gastroenterology* 2003; **124**: 634-641 [PMID: 12612902 DOI: 10.1053/gast.2003.50088]

78 **Singh V**, Dheerendra PC, Singh B, Nain CK, Chawla D, Sharma N, Bhalla A, Mahi SK. Midodrine versus albumin in the prevention of paracentesis-induced circulatory dysfunction in cirrhotics: a randomized pilot study. *Am J Gastroenterol* 2008; **103**: 1399-1405 [PMID: 18547224 DOI: 10.1111/j.1572-0241.2008.01787.x]

79 **Sersté T**, Melot C, Francoz C, Durand F, Rautou PE, Valla D, Moreau R, Lebrec D. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 2010; **52**: 1017-1022 [PMID: 20583214 DOI: 10.1002/hep.23775]

80 **Rössle M**, Ochs A, Gülberg V, Siegerstetter V, Holl J, Deibert P, Olschewski M, Reiser M, Gerbes AL. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med* 2000; **342**: 1701-1707 [PMID: 10841872 DOI: 10.1056/NEJM200006083422303]

81 **Boyer TD**, Haskal ZJ. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Hepatology* 2005; **41**: 386-400 [PMID: 15660434 DOI: 10.1002/hep.20559]

82 **Lebrec D**, Giuily N, Hadengue A, Vilgrain V, Moreau R, Poynard T, Gadano A, Lassen C, Benhamou JP, Erlinger S. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. French Group of Clinicians and a Group of Biologists. *J Hepatol* 1996; **25**: 135-144 [PMID: 8878773 DOI: 10.1016/S0168-8278(96)80065-1]

83 **Boyer TD**, Haskal ZJ. The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009. *Hepatology* 2010; **51**: 306 [PMID: 19902484 DOI: 10.1002/hep.23383]

84 **D'Amico G**, Luca A, Morabito A, Miraglia R, D'Amico M. Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis. *Gastroenterology* 2005; **129**: 1282-1293 [PMID: 16230081 DOI: 10.1053/j.gastro.2005.07.031]

85 **Quiroga J**, Sangro B, Núñez M, Bilbao I, Longo J, García-Villarreal L, Zozaya JM, Betés M, Herrero JI, Prieto J. Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites: effect on clinical, renal, humoral, and hemodynamic parameters. *Hepatology* 1995; **21**: 986-994 [PMID: 7705810 DOI: 10.1016/0270-9139(95)90245-7]

86 **Colapinto RF**, Stronell RD, Gildiner M, Ritchie AC, Langer B, Taylor BR, Blendis LM. Formation of intrahepatic portosystemic shunts using a balloon dilatation catheter: preliminary clinical experience. *AJR Am J Roentgenol* 1983; **140**: 709-714 [PMID: 6601376 DOI: 10.2214/ajr.140.4.709]

87 **Riggio O**, Angeloni S, Salvatori FM, De Santis A, Cerini F, Farcomeni A, Attili AF, Merli M. Incidence, natural history, and risk factors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stent grafts. *Am J Gastroenterol* 2008; **103**: 2738-2746 [PMID: 18775022 DOI: 10.1111/j.1572-0241.2008.02102.x]

88 **Bureau C**, Pagan JC, Layrargues GP, Metivier S, Bellot P, Perreault P, Otal P, Abraldes JG, Peron JM, Rousseau H, Bosch J, Vinel JP. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. *Liver Int* 2007; **27**: 742-747 [PMID: 17617116 DOI: 10.1111/j.1478-3231.2007.01522.x]

89 **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 [PMID: 3395243]

90 **Salerno F**, Merli M, Riggio O, Cazzaniga M, Valeriano V, Pozzi M, Nicolini A, Salvatori F. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. *Hepatology* 2004; **40**: 629-635 [PMID: 15349901 DOI: 10.1002/hep.20364]

91 **Plauth M**, Schütz T, Buckendahl DP, Kreymann G, Pirlich M, Grüngreiff S, Romaniuk P, Ertl S, Weiss ML, Lochs H. Weight gain after transjugular intrahepatic portosystemic shunt is associated with improvement in body composition in malnourished patients with cirrhosis and hypermetabolism. *J Hepatol* 2004; **40**: 228-233 [PMID: 14739092 DOI: 10.1016/j.jhep.2003.10.011]

92 **Campbell MS**, Brensinger CM, Sanyal AJ, Gennings C, Wong F, Kowdley KV, McCashland T, Reddy KR. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. *Hepatology* 2005; **42**: 635-640 [PMID: 16108073 DOI: 10.1002/hep.20840]

93 **Montgomery A**, Ferral H, Vasan R, Postoak DW. MELD score as a predictor of early death in patients undergoing elective transjugular intrahepatic portosystemic shunt (TIPS) procedures. *Cardiovasc Intervent Radiol* 2005; **28**: 307-312 [PMID: 15886944 DOI: 10.1007/s00270-004-0145-y]

94 **Sanyal AJ**, Freedman AM, Luketic VA, Purdum PP, Shiffman ML, DeMeo J, Cole PE, Tisnado J. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. *Gastroenterology* 1997; **112**: 889-898 [PMID: 9041251 DOI: 10.1053/gast.1997.v112.pm9041251]

95 **Guevara M**, Ginès P, Bandi JC, Gilabert R, Sort P, Jiménez W, Garcia-Pagan JC, Bosch J, Arroyo V, Rodés J. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998; **28**: 416-422 [PMID: 9696006 DOI: 10.1002/hep.510280219]

96 **Becker G**, Galandi D, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. *J Pain Symptom Manage* 2007; **34**: 547-565 [PMID: 17900855]

97 **Moskovitz M**. The peritoneovenous shunt: expectations and reality. *Am J Gastroenterol* 1990; **85**: 917-929 [PMID: 2197858]

98 **Pockros PJ**, Esrason KT, Nguyen C, Duque J, Woods S. Mobilization of malignant ascites with diuretics is dependent on ascitic fluid characteristics. *Gastroenterology* 1992; **103**: 1302-1306 [PMID: 1397889]

99 **Scholz DG**, Nagorney DM, Lindor KD. Poor outcome from peritoneovenous shunts for refractory ascites. *Am J Gastroenterol* 1989; **84**: 540-543 [PMID: 2719011]

100 **Gur C**, Ilan Y, Shibolet O. Hepatic hydrothorax--pathophysiology, diagnosis and treatment--review of the literature. *Liver Int* 2004; **24**: 281-284 [PMID: 15287850 DOI: 10.1111/j.1478-3231.2004.0936.x]

101 **Huang PM**, Chang YL, Yang CY, Lee YC. The morphology of diaphragmatic defects in hepatic hydrothorax: thoracoscopic finding. *J Thorac Cardiovasc Surg* 2005; **130**: 141-145 [PMID: 15999054 DOI: 10.1016/j.jtcvs.2004.08.051]

102 **Miserocchi G**. Physiology and pathophysiology of pleural fluid turnover. *Eur Respir J* 1997; **10**: 219-225 [PMID: 9032518 DOI: 10.1183/09031936.97.10010219]

103 **Light RW**, Macgregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972; **77**: 507-513 [PMID: 4642731]

104 **Xiol X**, Castellví JM, Guardiola J, Sesé E, Castellote J, Perelló A, Cervantes X, Iborra MJ. Spontaneous bacterial empyema in cirrhotic patients: a prospective study. *Hepatology* 1996; **23**: 719-723 [PMID: 8666323 DOI: 10.1002/hep.510230410]

105 **Runyon BA**, Greenblatt M, Ming RH. Hepatic hydrothorax is a relative contraindication to chest tube insertion. *Am J Gastroenterol* 1986; **81**: 566-567 [PMID: 3717119]

106 **Gordon FD**, Anastopoulos HT, Crenshaw W, Gilchrist B, McEniff N, Falchuk KR, LoCicero J, Lewis WD, Jenkins RL, Trey C. The successful treatment of symptomatic, refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt. *Hepatology* 1997; **25**: 1366-1369 [PMID: 9185754 DOI: 10.1002/hep.510250611]

107 **Siegerstetter V**, Deibert P, Ochs A, Olschewski M, Blum

HE, Rössle M. Treatment of refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt: long-term results in 40 patients. *Eur J Gastroenterol Hepatol* 2001; **13**: 529-534 [PMID: 11396532 DOI: 10.1097/00042737-200105000-00011]

108 **Milanez de Campos JR**, Filho LO, de Campos Werebe E, Sette H, Fernandez A, Filomeno LT, Jatene FB. Thoracoscopy and talc poudrage in the management of hepatic hydrothorax. *Chest* 2000; **118**: 13-17 [PMID: 10893352 DOI: 10.1378/chest.118.1.13]

109 **Lameire N**, Van Biesen W, Vanholder R. Acute renal failure. *Lancet* 2005; **365**: 417-430 [PMID: 15680458 DOI: 10.1016/S0140-6736(05)70238-5]

110 **Hampel H**, Bynum GD, Zamora E, El-Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. *Am J Gastroenterol* 2001; **96**: 2206-2210 [PMID: 11467654 DOI: 10.1111/j.1572-0241.2001.03958.x]

111 **Ginès P**, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJMra0809139]

112 **Clària J**, Kent JD, López-Parra M, Escolar G, Ruiz-Del-Arbol L, Ginès P, Jiménez W, Vucelic B, Arroyo V. Effects of celecoxib and naproxen on renal function in nonazotemic patients with cirrhosis and ascites. *Hepatology* 2005; **41**: 579-587 [PMID: 15723448 DOI: 10.1002/hep.20595]

113 **Pariente EA**, Bataille C, Bercoff E, Lebrec D. Acute effects of captopril on systemic and renal hemodynamics and on renal function in cirrhotic patients with ascites. *Gastroenterology* 1985; **88**: 1255-1259 [PMID: 3884428]

114 **Guevara M**, Fernández-Esparrach G, Alessandria C, Torre A, Terra C, Montañà X, Piera C, Alvarez ML, Jiménez W, Ginès P, Arroyo V. Effects of contrast media on renal function in patients with cirrhosis: a prospective study. *Hepatology* 2004; **40**: 646-651 [PMID: 15349903 DOI: 10.1002/hep.20531]

115 **Wadei HM**, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol* 2006; **1**: 1066-1079 [PMID: 17699328 DOI: 10.2215/CJN.01340406]

116 **Magan AA**, Khalil AA, Ahmed MH. Terlipressin and hepatorenal syndrome: what is important for nephrologists and hepatologists. *World J Gastroenterol* 2010; **16**: 5139-5147 [PMID: 21049548]

117 **Hadengue A**, Gadano A, Moreau R, Giostra E, Durand F, Valla D, Erlinger S, Lebrec D. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J Hepatol* 1998; **29**: 565-570 [PMID: 9824265]

118 **Neri S**, Pulvirenti D, Malaguarnera M, Cosimo BM, Bertino G, Ignaccolo L, Siringo S, Castellino P. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. *Dig Dis Sci* 2008; **53**: 830-835 [PMID: 17939047]

119 **Alessandria C**, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, Balzola F, Morgando A, Rizzetto M, Marzano A. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007; **47**: 499-505 [PMID: 17560680]

120 **Gluud LL**, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010; **51**: 576-584 [PMID: 19885875 DOI: 10.1002/hep.23286]

121 **Ortega R**, Ginès P, Uriz J, Cárdenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jiménez W, Arroyo V, Rodés J. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology* 2002; **36**: 941-948 [PMID: 12297842 DOI: 10.1053/jhep.2002.35819]

122 **Skagen C**, Einstein M, Lucey MR, Said A. Combination treatment with octreotide, midodrine, and albumin improves survival in patients with type 1 and type 2 hepatorenal syndrome. *J Clin Gastroenterol* 2009; **43**: 680-685 [PMID: 19238094 DOI: 10.1097/MCG.0b013e318188947c]

123 **Salerno F**, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; **56**: 1310-1318 [PMID: 17389705]

124 **Angeli P**, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, Amodio P, Sticca A, Caregaro L, Maffei-Faccioli A, Gatta A. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999; **29**: 1690-1697 [PMID: 10347109 DOI: 10.1002/hep.510290629]

125 **Wong LP**, Blackley MP, Andreoni KA, Chin H, Falk RJ, Klemmer PJ. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int* 2005; **68**: 362-370 [PMID: 15954928 DOI: 10.1111/j.1523-1755.2005.00408.x]

126 **Alessandria C**, Ozdogan O, Guevara M, Restuccia T, Jiménez W, Arroyo V, Rodés J, Ginès P. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 2005; **41**: 1282-1289 [PMID: 15834937]

127 **Said A**, Williams J, Holden J, Remington P, Gangnon R, Musat A, Lucey MR. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol* 2004; **40**: 897-903 [PMID: 15158328 DOI: 10.1016/j.jhep.2004.02.010]

128 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]

129 **Moylan CA**, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008; **300**: 2371-2378 [PMID: 19033587 DOI: 10.1001/jama.2008.720]

130 **Dutkowski P**, Oberkofler CE, Béchir M, Müllhaupt B, Geier A, Raptis DA, Clavien PA. The model for end-stage liver disease allocation system for liver transplantation saves lives, but increases morbidity and cost: a prospective outcome analysis. *Liver Transpl* 2011; **17**: 674-684 [PMID: 21618688 DOI: 10.1002/lt.22228]

131 **Merion RM**, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. *Am J Transplant* 2005; **5**: 307-313 [PMID: 15643990 DOI: 10.1111/j.1600-6143.2004.00703.x]

132 **Thompson JA**, Lake JR. The impact of MELD allocation on simultaneous liver-kidney transplantation. *Curr Gastroenterol Rep* 2009; **11**: 76-82 [PMID: 19166663 DOI: 10.1007/s11894-009-0012-8]

133 **Nadim MK**, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, Feng S, Friedewald JJ, Hong JC, Kellum JA, Kim WR, Lake JR, Melton LB, Pomfret EA, Saab S, Genyk YS. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant* 2012; **12**: 2901-2908 [PMID: 22822723 DOI: 10.1111/j.1600-6143.2012.04176.x]

P- Reviewers Pai CG, Singh V **S- Editor** Gou SX **L- Editor** A **E- Editor** Li JY