JEIMP
THE SCIENCE
Journal of
European Internal Medicine Professionals
J Eur Int Med Prof
2023, Volume 1(2)

10.5281/zenodo.7772708

Review

Hepatorenal Syndrome: A Mini Review

Atilla Bulur
Gastroenterology and Endoscopy Private Clinic, Aydın, Turkey

Corresponding author: Atilla Bulur, Gastroenterology and Endoscopy Private Clinic, Kurtuluş Mah. 348 Sok. No:56, Nazilli, Aydın, Türkiye
E-mail: atillabulur@hotmail.com
Cite this article: Bulur A. Hepatorenal Syndrome: A Mini Review. *J Eur Int Med Prof.* 2023;1(2):39-44.

Received: 17.02.2023 **Accepted**: 26.02.2023 **Published**: 27.03.2023

ABSTRACT

Hepatorenal syndrome (HRS) is diagnosed in individuals who have no etiologic factors for the development of renal disease other than the chronic decompensated liver disease (DLD). HRS represents the end stage of a series of reductions in renal blood flow caused by progressive severe liver injury. HRS is a strong indicator of morbidity and mortality in these patients. A specific treatment approach for HRS is not available because the mechanisms underlying the development of renal dysfunction are not clear. Because of the severe circulatory abnormality and portal hypertension in the background of the clinical aspect, HRS is the most life-threatening entity in DLD patients with acute renal dysfunction.

Keywords: Hepatorenal syndrome, chronic liver disease, kidney failure

ETIOPATHOGENESIS

The relationship between liver disease and renal failure has been known for more than a hundred years (1-3). Flint noted that in most cases of renal failure in cirrhosis, no significant histologic changes were found in the kidneys at autopsy (3). Hecker and Sherlock in 1956 noted progressive oliguria, very low urinary sodium excretion, and hyponatremia and described nine patients with liver disease in the absence of proteinuria and renal failure (4). In addition, it was found that renal failure was functional in these patients and other patients with chronic renal failure. In these patients, renal failure improved after treatment with liver transplantation.

In 1996, the International Acid Club defined the definition and diagnostic criteria for HRS, and the term is generally accepted for functional renal failure that develops in patients with DLD (1-5). Patients who develop HRS are usually patients with DLD, severe alcoholic hepatitis, or less commonly, patients with portal hypertension due to metastatic tumors and fulminant liver failure from any cause (6-8). Portal hypertension in patients with cirrhosis causes numerous complications. It has been reported that splanchnic vasodilation resulting from portal hypertension plays an important role in renal injury. One of themost important mechanisms is the increase of vasodilators such as nitric oxide in the splanchnic circulation (6,9,10). As cirrhosis decompensates, there is a progressive increase in cardiac output and a decrease in systemic vascular resistance. The second change is thought to be due in part to hypotension-induced activation of the renin-angiotensin and sympathetic nervous systems (7,11) (**Figure 1**).

Bacterial translocation from the intestine to the mesenteric lymph nodes may play an important role in this process (**Figure 1**) (12-15).

EPIDEMIOLOGY and CLINICAL MANIFESTATIONS

Incidence of HRS, in a prospective study of 229 patients without renal failure with DLD and ascites: HRS developed in 18 percent and 39 percent of patients at one and five years, respectively. Patients with hyponatremia and high plasma renin activity were found to be at the highest risk (12). Usually, HRS develops in patients with advanced cirrhosis, so patients experience other manifestations of chronic liver disease such as jaundice, clubbing, palmar erythema, gynecomastia, temporal wasting, and spider nevus. Also, other clinical features include splenomegaly, bleeding tendency, hepatic encephalopathy, edema, and ascites. Patients usually have lower arterial blood pressure and wider pulse pressure.

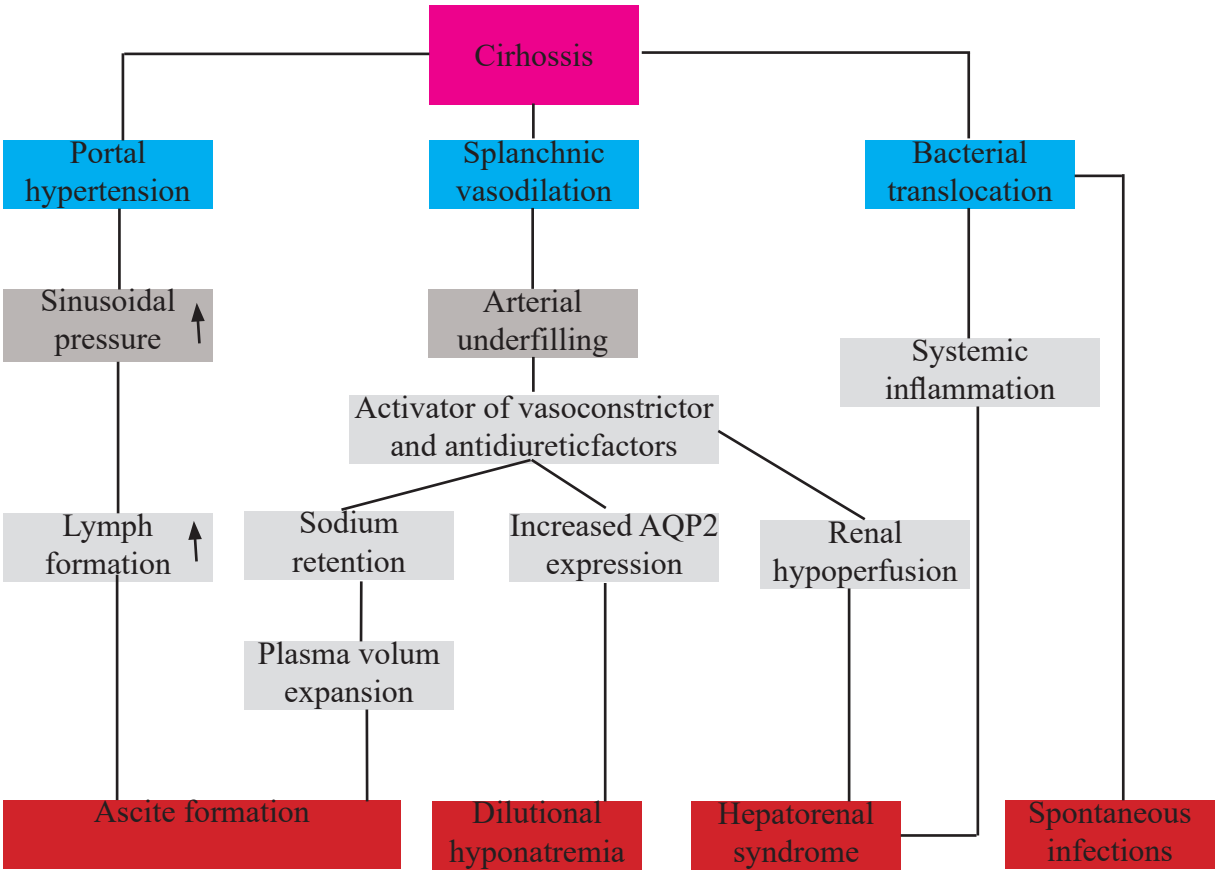

Figure 1. Pathogenesis of ascites and related complications of cirrhosis (adapted from reference 14), AQP2;

Urinary output is greatly reduced, especially in type 1 HRS. HRS rarely occurs in patients with early and well-compensated disease. The risk of HRS is increased in patients with refractory acid, defined as unresponsiveness to high-dose diuretics (spironolactone 400 mg daily and furosemide 160 mg daily) (1,5).

DIAGNOSIS

HRS is characterized by the following features in a patient with DLD (acute or chronic liver disease) (**Table 1**). Many patients with HRS are nonoliguric (especially early in the course of the disease) (6-8).

Table 1. Characteristic of hepatorenal syndrome

• Progressive increase in serum creatinine
• Usually normal urine sediment
• No or little proteinuria (less than 500 mg per day)
• Low sodium excretion rate (urine sodium concentration is often less than 10 mEq/L)
• Nonoliguria or oliguria depending on its severity and duration

Two forms of HRS have been described, depending on the rate of decline in renal function (5);

1.Hepatorenal Syndrome Type 1 (HRS-AKI): This more severe form of HRS is traditionally referred to as hepatorenal syndrome - acute kidney injury (HRS-AKI) or type 1 HRS. It is defined as at least a twofold increase in serum creatinine (sCr) (reflecting a 50 percent decrease in creatinine clearance) to a level greater than 2.5 mg/dL in less than two weeks. GFR is usually less than 20 mL/min. Median survival is less than 2 weeks, and virtually all patients die within 8-10 weeks of the onset of renal failure.

2.Hepatorenal syndrome type 2 (diuretic-resistant acid): Type 2 HRS is defined as milder renal dysfunction than is observed in type 1 HRS. The main clinical feature in patients with type 2 HRS is ascites resistant to diuretics. Patients have a longer median survival time of approximately 6 months.

HRS is a diagnosis of exclusion, meaning that patients with DLD must be shown to have no acute or subacute renal injury before the diagnosis of HRS is made. The onset of renal failure is usually insidious, but can be HRS triggered by a bacterial infection (e.g., spontaneous bacterial peritonitis) or gastrointestinal bleeding. At HRS, renal dysfunction may be much more severe than the sCr value suggests. Creatinine is the most practical and common marker for the assessment of renal function. However, assessment of renal function by sCR in cirrhosis is limited because of low muscle volume and impaired formation of creatinine from creatine (synthesized by the liver) in muscle cells and dilute sCr due to excessive water accumulation (16). Because there are several underlying conditions that falsely contribute

to low sCr concentrations in patients with cirrhosis, even in the presence of moderate to severe renal dysfunction, creatinine-based methods often lead to overestimation of true GFR. Even in the presence of moderate to severe renal dysfunction, creatinine-based methods overestimate true GFR by 95% in patients with cirrhosis in published studies (16,17). Therefore, the introduction of a fixed threshold for sCr of 1.5 mg/dl in patients with cirrhosis may not be accurate (5,18). However, this definition may also strongly explain the mortality of cirrhotic patients who die in hospital (19,20).

The Kidney Disease Improving Global Outcome (KDIGO) proposed the acute kidney injury (AKI) criteria by combining the parts of the Acute Dialysis Quality Initiative group for the risk, injury, failure, loss of renal function, and end-stage renal disease criteria (RIFLE) and the Acute Kidney Injury Network group (AKIN) for the AKIN criteria (**Table 2**) (21-23).

Cirrhosis and its complications are summarized in **Figure 1.** Portal hypertension, splanchnic vasodilation, and bacterial translocation are considered the most important pathogenesis factors. One of the complications that develop at the end of this complex cascade is the formation of HRS (15).

DIFFERENTIAL DIAGNOSIS

The diagnosis of HRS may be made after other causes of acute or subacute renal injury have been excluded. For example, both glomerulonephritis and vasculitis can occur in patients with liver disease and should be suspected in patients with active urinary sediment. Most patients with liver cirrhosis due to obesity with fatty liver have diabetes and may develop diabetic nephropathy. A prospective study examining 562 patients with cirrhosis and renal dysfunction at a single center found that HRS occurred less frequently than prerenal or infection-related renal damage (13%, 32%, and 46%, respectively) (24).

Patients with DLD may develop acute tubular necrosis (ATN) if aminoglycoside therapy, radiocontrast agent therapy, sepsis, or hypotension are present. Suspicion of ATN arises from the history and the rapid rise in sCr as opposed to the normally gradual rise in HRS (5). Some of the conventional laboratory methods used to differentiate between prerenal disease and ATN may not be helpful in patients with cirrhosis. For example, it is associated with fractional sodium excretion of more than 2 percent in ATN and granular and epithelial cells in urinary sediment. On the other hand, in patients with cirrhosis who develop ATN due to renal ischemia, fractional sodium excretion may remain below 1%.

It can be difficult to distinguish hepatorenal syndrome from prerenal azotemia. In patients with cirrhosis, the prerenal disease may be precipitated by gastrointestinal fluid loss, bleeding, or treatment with a diuretic or nonsteroidal anti-inflammatory drug. (6,25)

Beta-blockers are used to prevent varices in patients with DLD. However, these agents can be dangerous in patients with ascites and hypotension, and their discontinuation can lead to the resolution of the overt HRS (26).

TREATMENT

The most important thing in the treatment of HRS; is the normalization of liver functions, i.e., the treatment of DLD. The ability to avoid alcohol in patients with alcoholic liver disease and HRS improves with follow-up of patients with chronic hepatitis B with antiviral treatments is remarkable (27,28). HRS hepatitis B, especially type 1, was considered a rapid and fatal complication of DLD if liver transplantation could not be performed immediately. Fortunately, as knowledge

Table 2. KDIGO, RIFLE, and AKIN AKI diagnostic criteria

RIFLE	AKIN	KDIGO	Urine Uutput
Risk: sCr increase; 1.5- to 2-fold from baseline or GFR decrease > 25%	Stage 1: sCr increase 1.5-1.9 times from baseline or ≥ 0.3 mg/dl increase within 48 h	Stage 1: sCr increase × 1.5 baseline or GFR decrease > 25%	< 0.5 ml/kg/h for 6-12 h
Injury: sCr increase; 2.0-2.9 times from baseline or GFR decrease > 50%	Stage 2: sCr increase > 2- to 3-fold from baseline	Stage 2: sCr increase × 2 from baseline or GFR decreased >50%	< 0.5 ml/kg/h for 12 h
Failure: sCr increase; ≥ 3 times from baseline or GFR decrease > 75% or sCr ≥ 4 mg/dl	Stage 3: sCr increased > 300% (>3-fold) from baseline, or ≥ 4.0 mg/dl with an acute increase of ≥ 0.5 mg/dl or on renal replacement therapy	Stage 3: Increase × 3 from baseline or sCr > 4 mg/dl) with an acute rise > 0.5 mg/dl or GFR decreased > 75%	< 0.3 ml/kg/h for 24 h or anuria for 12 h
Loss:Persistan Acute Kidney Failure: Complete loss of kidney function > 4 weeks			
ESKD: End-stage kidney disease (complete loss of kidney function > 3 months)			

sCr; serum creatinine, KDIGO; Kidney Disease Improving Global Outcomes, RIFLE; The Risk, Injury, Failure, Loss, End-Stage, AKIN; Acute Kidney Injury Network

of the pathogenesis increased, medical treatments were discovered that improved short-term outcomes. In addition, new pharmacological treatments have been developed that improve the feasibility of liver transplantation in eligible patients with HRS (1).

Numerous pharmacological agents have been tried for the treatment of HRS. The use of renal vasodilators (dopamine and prostaglandin analogues) cannot be used because of insufficient data to confirm their side effects and benefits. They are the best pharmacological treatment today, as studies with systemic vasoconstrictors have confirmed a beneficial role at HRS. They were first used in 1998, and their effect is to improve renal function by suppressing arterial splanchnic vasodilation and activating the endogenous vasoconstrictor system (29,30).

If short-term improvement in liver function is not possible, drug treatment should be initiated to try to reverse the acute renal injury associated with HRS. In general, patients who are not candidates for liver transplantation are not followed up in the ICU. Type 1 HRS commonly develops in patients with DLD but can also occur in patients with acute liver failure. Fluid intake, blood chemistry, and urine output must be monitored closely. In case of dilutional hyponatremia, a fluid restriction of 1 liter per day is recommended (31). The use of diuretics in HRS can lead to electrolyte imbalance (hyperkalemia and hyponatremia) and therefore requires very careful evaluation. Patients with type 2 HRS usually have a milder course and can be treated as outpatients.

All antihypertensive agents, including beta-blockers, should be discontinued in patients with HRS. In patients with HRS, treated in the intensive care unit, norepinephrine with albumin is recommended as initial therapy. Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/hour) to increase mean arterial pressure by 10 mmHg, and albumin is given as an intravenous bolus (1 g/kg per day). Intravenous vasopressin may also be effective, starting at 0.01 units/min and titrated as needed to increase mean arterial pressure.

Combination therapy with terlipressin and albumin is recommended for HRS patients who are in the intensive care unit. Terlipressin is administered as an intravenous bolus (1 to 2 mg every four to six hours) and albumin is administered as an intravenous bolus (1 g/kg per day).

In cases where terlipressin therapy is not possible, a combination of midodrine, octreotide, and albumin may be used as initial therapy. Midodrine is given orally (starting at 7.5 mg, increasing to a maximum of 15 mg orally three times daily at 8-hour intervals), octreotide is given either as a continuous intravenous infusion (50 mcg/hour) or subcutaneously (100 to 200 mcg daily), and albumin is given as an intravenous bolus (1 g/kg per day) for two days, then 25-50 g per day until midodrine and octreotide treatment are discontinued.

In selected patients who do not respond to medical treatments, a transjugular intrahepatic portosystemic shunt (TIPS) can sometimes be successful. However, complications associated with TIPS can occur: increased rate of hepatic encephalopathy, deterioration worsening of liver function, renal injury associated with intravenous contrast, and bleeding complications after the complication of procedure (32). For this reason, some clinicians prefer dialysis as the first choice, especially in patients whose sCr remains above 1.5 mg/dL despite medical treatment. Patients with HRS, who develop renal failure, can be treated with renal replacement therapy (hemodialysis or continuous venovenous hemofiltration). In two retrospective studies, 30-50% of transplant candidates who developed acute kidney injury and required dialysis survived following liver transplantation (33,34).

In patients with HRS, acute renal injury is expected to be treated with drug therapy or TIPS. In addition, treatment with norepinephrine, terlipressin, or midodrine plus octreotide aims to increase mean arterial pressure by approximately 10 to 15 mmHg. A systematic review of 501 patients with HRS from 21 studies found a significant association between the increase in mean arterial pressure caused by these vasoconstrictors and the decrease in sCr (35).

Liver transplantation or dialysis treatment is recommended in patients who do not respond to the treatments listed above, whose kidney functions do not improve, and who are candidates for liver transplantation (36,37). The most common liver transplantation indication is DLD, followed by hepatocellular carcinoma and acute liver failure (38,39).

In the 10-year follow-up of 62 patients who underwent liver transplantation due to type 1 HRS, in a single center; While the mean sCr was 3.4 mg/dL before transplantation, it was determined that HRS improved (sCr<1.5 mg/dL) after transplantation and the number of patients who did not need dialysis was 47 (76%). The remaining patients either died or required chronic dialysis (40).

Administration of albumin in patients with spontaneous bacterial peritonitis may prevent the development of HRS, and in patients with acute alcoholic hepatitis, the use of pentoxifylline, a TNF inhibitor, has been shown to reduce the incidence and mortality of HRS compared to the control group (19,41).

Medications such as misoprostol, N-acetylcysteine, and angiotensin-converting enzyme inhibitors have been

tried for the treatment of HRS. No significant treatment response associated with these treatments has been obtained, so they are not recommended. In rare patients, a peritoneovenous shunt is used. Peritoneovenous shunt is the treatment method that provides drainage of ascites from the peritoneum to the internal jugular vein. This therapy has been used in patients with refractory ascites and renal failure due to HRS. In addition, the increase in fluid return to the systemic circulation with shunt therapy may lead to a decrease in the activity of sodium retention and vasoconstrictive mechanisms, and a moderate increase in GFR, respectively (42).

PROGNOSIS

HRS is a life-threatening complication of DLD. The mortality of patients with liver failure increases significantly if HRS develops. Untreated or unresponsive to treatment, most patients die within weeks of the onset of renal dysfunction. In contrast, some patients with HRS can have their kidney and liver dysfunctions returned to normal with medical, surgical (TIPS, shunt) or liver transplantation (43).

With increasing knowledge of liver cirrhosis, portal hypertension, ascites, as well as HRS, new pharmacological treatments such as terlipressin and albumin administration have proven beneficial in improving the short-term outcomes of HRS. Future treatment of HRS will likely target multiple aspects of the pathophysiological process (1).

Liver transplantation is the definitive treatment for HRS. However, type 1 HRS is an emergency and many patients may die before surgery, as they have a short survival time versus a long waiting time in most centers. If liver transplantation is feasible, the probability of 3-year post-transplant survival in HRS patients treated with terlipressin and albumin is similar to that of patients with cirrhosis without HRS (44).

In a prospective study of 272 patients with cirrhosis; Acute kidney disease developed in 80 patients (29%) within five years. Of these, 42 patients (52%) recovered, and 16 (38%) of these patients had relapsed acute kidney disease. Of all patients, 11 patients with acute kidney disease (14%) progressed to chronic kidney disease and 36 patients (45%) died (45).

CONCLUSION

HRS is an important cause of morbidity and mortality in patients with chronic liver disease. In cases of renal failure that may develop in these patients, HRS should be kept in mind in the differential diagnosis. HRS treatment can be performed medically (such as terlipressin and albumin), through dialysis, and surgically (including liver transplantation) with success. Therefore, early diagnosis and treatment are very important for the prognosis of the disease.

DISCLOSURES

Ethics Committee Approval Number: Not necessary.
Informed Consent: Not necessary.
Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: Authors declare no conflict of interest.
Author Contributions: A.B. interpreting and submitting to Journal. The author read and agreed to the published version of the manuscript.

REFERENCES

1.Ng CK, Chan MH, Tai MH, Lam CW. Hepatorenal syndrome. *Clin Biochem Rev*. 2007;28(1):11-17.
2.Frerichs FT. Tratado practico de las Enfermedades del Higado, *de los Vasos Hepaticos y de las Vias Biliares*. Madrid: Libreria Extranjera y Nacional, cientifica y Literaria,
3.Flint A. Clinical report on hydro-peritoneum based on an analysis of forty-six cases. *Am J Med Sci*. 1863;45:306–39.
4.Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. *Lancet*. 1956;271(6953):1121-1125. doi:10.1016/s0140-6736(56)90149-0
5.Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology*. 1996;23(1):164-176. doi:10.1002/hep.510230122
6.Ginès P, Schrier RW. Renal failure in cirrhosis [published correction appears in N Engl J Med. 2011 Jan 27;364(4):389]. *N Engl J Med.* 2009;361(13):1279-1290. doi:10.1056/NEJMra0809139
7.Wadei HM, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol*. 2006;1(5):1066-1079. doi:10.2215/CJN.01340406
8.Ginès P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. *Lancet*. 2003;362(9398):1819-1827. doi:10.1016/S0140-6736(03)14903-3
9.Martin PY, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med*. 1998;339(8):533-541. doi:10.1056/NEJM199808203390807
10.Iwakiri Y. The molecules: mechanisms of arterial vasodilatation observed in the splanchnic and systemic circulation in portal hypertension. *J Clin Gastroenterol.* 2007;41 Suppl 3:S288-S294. doi:10.1097/MCG.0b013e3181468b4c
11.Fernandez-Seara J, Prieto J, Quiroga J, et al. Systemic and regional hemodynamics in patients with liver cirrhosis and ascites with and without functional renal failure. *Gastroenterology*. 1989;97(5):1304-1312. doi:10.1016/0016-5085(89)91704-6
12.Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology*. 1993;105(1):229-236. doi:10.1016/0016-5085(93)90031-7
13.Runyon BA, Squier S, Borzio M. Translocation of gut bacteria in rats with cirrhosis to mesenteric lymph nodes partially explains the pathogenesis of spontaneous bacterial peritonitis. *J Hepatol.* 1994;21(5):792-796. doi:10.1016/s0168-8278(94)80241-6
14.Wiest R, Das S, Cadelina G, Garcia-Tsao G, Milstien S, Groszmann RJ. Bacterial translocation in cirrhotic rats stimulates eNOS-derived NO production and impairs mesenteric vascular contractility. *J Clin Invest*. 1999;104(9):1223-1233. doi:10.1172/JCI7458
15.Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74(2):1014-1048. doi:10.1002/hep.31884
16.Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J Kidney Dis*. 2003;41(2):269-278. doi:10.1053/ajkd.2003.50035
17.Caregaro L, Menon F, Angeli P, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. *Arch Intern Med.* 1994;154(2):201-205
18.SSalerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56(9):1310-1318. doi:10.1136/gut.2006.107789
19.Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on

renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341(6):403-409. doi:10.1056/NEJM199908053410603
20.Angeli P, Fasolato S, Mazza E, et al. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial. *Gut*. 2010;59(1):98-104. doi:10.1136/gut.2008.176495
21.Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212. doi:10.1186/cc2872
22.Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31. doi:10.1186/cc5713
23.Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825-830. doi:10.7326/0003-4819-158-11-201306040-00007)
24.Martín-Llahí M, Guevara M, Torre A, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology*. 2011;140(2):488-496.e4. doi:10.1053/j.gastro.2010.07.043
25.Laffi G, Daskalopoulos G, Kronborg I, Hsueh W, Gentilini P, Zipser RD. Effects of sulindac and ibuprofen in patients with cirrhosis and ascites. An explanation for the renal-sparing effect of sulindac. *Gastroenterology*. 1986;90(1):182-187. doi:10.1016/0016-5085(86)90091-0
26.de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension [published correction appears in J Hepatol. 2022 Apr 14;:]. *J Hepatol*. 2022;76(4):959-974. doi:10.1016/j.jhep.2021.12.022
27.Amini M, Runyon BA. Alcoholic hepatitis 2010: a clinician's guide to diagnosis and therapy. *World J Gastroenterol.* 2010;16(39):4905-4912. doi:10.3748/wjg.v16.i39.4905
28. Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure [published correction appears in Hepatology. 2011 Sep 2;54(3):1114]. *Hepatology*. 2011;53(3):774-780. doi:10.1002/hep.24109
29.Piano S, Tonon M, Angeli P. Management of ascites and hepatorenal syndrome. *Hepatol Int*. 2018;12(Suppl 1):122-134. doi:10.1007/s12072-017-9815-0
30.Guevara M, Ginès P, Fernández-Esparrach G, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology*. 1998;27(1):35-41. doi:10.1002/hep.510270107
31.Cardenas A, Gines P. Pathogenesis and treatment of dilutional hyponatraemia in cirrhosis. In: Arroyo V, Forns X, Garcia-Pagan JC, Rodes J, editors. *Progress in the treatment of liver diseases*. Barcelona: Ars Medica, 2003. p. 31–42.
32.Rössle M, Gerbes AL. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. *Gut*. 2010;59(7):988-1000. doi:10.1136/gut.2009.193227
33.Allegretti AS, Parada XV, Eneanya ND, et al. Prognosis of Patients with Cirrhosis and AKI Who Initiate RRT. *Clin J Am Soc Nephrol*. 2018;13(1):16-25. doi:10.2215/CJN.03610417
34.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(1):362-370. doi:10.1111/j.1523-1755.2005.00408.x
35.Velez JC, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. *Am J Kidney Dis*. 2011;58(6):928-938. doi:10.1053/j.ajkd.2011.07.017
36.Arroyo V, Guevara M, Ginès P. Hepatorenal syndrome in cirrhosis: pathogenesis and treatment. *Gastroenterology*. 2002;122(6):1658-1676. doi:10.1053/gast.2002.33575
37.Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome--experience in 300 patients. *Transplantation*. 1991;51(2):428-430. doi:10.1097/00007890-199102000-00030
38.European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol*. 2016;64(2):433-485. doi:10.1016/j.jhep.2015.10.006
39.Bulur A, Sevmiş M. Clinical, surgical and histopathological characteristics of liver transplant recipients: An analysis of a large sample from Turkey. *Gulhane Med J*. 2022; 64:60-6. doi: 10.4274/gulhane.galenos.2021.83803
40.Wong F, Leung W, Al Beshir M, Marquez M, Renner EL. Outcomes of patients with cirrhosis and hepatorenal syndrome type 1 treated with liver transplantation. *Liver Transpl*. 2015;21(3):300-307. doi:10.1002/lt.24049
41.Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119(6):1637-1648. doi:10.1053/gast.2000.20189
42.LLinas SL, Schaefer JW, Moore EE, Good JT Jr, Giansiracusa R. Peritoneovenous shunt in the management of the hepatorenal syndrome. *Kidney Int*. 1986;30(5):736-740. doi:10.1038/ki.1986.249
43.Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology*. 2005;41(6):1282-1289. doi:10.1002/hep.20687
44.Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. *J Hepatol*. 2004;40(1):140-146. doi:10.1016/j.jhep.2003.09.019
45.Tonon M, Rosi S, Gambino CG, et al. Natural history of acute kidney disease in patients with cirrhosis. *J Hepatol*. 2021;74(3):578-583. doi:10.1016/j.jhep.2020.08.037