CIRRHOTIC MANAGEMENT

SUMMARY

Approximately 26,000 patients with cirrhosis in the United States require intensive care each year with in-hospital mortality of greater than 50%, prolonged length of hospitalization, and a cost of over $1 billion.

RECOMMENDATIONS

- **Level 1**
  - **In Type 1 hepatorenal syndrome (HRS), Terlipressin (1 mg IV q 4–6 hrs) in combination with albumin should be considered. If serum creatinine does not decrease at least 25% after 3 days, the dose of terlipressin should be increased in a stepwise manner up to a maximum of 2 mg IV q 4 hrs. If patients do not respond, treatment should be discontinued within 14 days.**
- **Level 2**
  - **In patients with cirrhosis and ascites, sodium restriction (2000 mg per day) and diretic therapy (oral spironolactone with or without oral furosemide) should be implemented.**
  - **Oral midodrine has been shown to improve clinical outcomes and survival in patients with refractory ascites.**
  - **For large-volume paracenteses, an albumin infusion of 6-8 g per liter of fluid removed appears to improve survival.**
  - **Albumin infusion plus administration of vasoactive medications such as octreotide and midodrine should be considered in the treatment of type 1 HRS.**
  - **Patients with cirrhosis, ascites, and type 1 or type 2 HRS should have an expedited referral for liver transplantation.**
  - **Nonabsorbent disaccharides (i.e, lactulose) and rifaximin, dosed to achieve 2-3 bowel movements per day, are recommended for treating patients with hepatic encephalopathy.**
  - **The treatment for type 1 HRS is liver transplantation.**
- **Level 3**
  - **Post-paracentesis albumin infusion may not be necessary for a single paracentesis of less than 4 to 5 L.**
  - **Empiric antibiotic therapy for unproven infection in patients presenting with Type 1 HRS is not supported.**
  - **In the absence of documented adrenal insufficiency, steroid therapy in critically ill patients with cirrhosis is not recommended.**

INTRODUCTION

As the number of failing organ systems increase, so does mortality. Two failing organ systems increase the mortality to 55%, whereas patients who develop failure of three or more organs have almost 100% mortality. The development of ascites in the presence of cirrhosis and portal hypertension is associated with 50% mortality at 3 years. Sepsis and systemic inflammation result in acute deterioration of liver function. Tumor

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

necrosis factor-α, interleukin-6, and other markers of activation of the immune system play a key role in the pathogenesis of hepatocellular microcirculatory dysfunction in sepsis. Microcirculatory dysfunction results in high portal pressures and reduced hepatic blood flow, which further worsen liver function. Synthetic function of the liver is also inhibited and results in impaired synthesis of coagulation factors. Renal impairment is the most common extra-hepatic organ dysfunction, and is categorized into four main types: hepatorenal syndrome (HRS), hypovolemia-induced, parenchymal disease, and drug-induced. Bacterial infection is a major risk factor for the development of any type of renal dysfunction, but especially of HRS, and is the most common precipitant of renal failure in cirrhosis. Adrenal insufficiency is reported in 51-68% of patients with cirrhosis and severe sepsis and is associated with increased mortality compared to patients without adrenal insufficiency. Acute respiratory consequences of cirrhosis include portopulmonary hypertension, and hepatopulmonary syndrome (HPS) may be encountered in cirrhotic patients. Exaggerated inflammatory response, coupled with a relative immunocompromised state predisposes to acute lung injury. Decreased thoracic compliance resulting from ascites, chest wall edema, and pleural effusion also plays a role in respiratory compromise in the cirrhotic patient. The risk of aspiration pneumonia is high because of altered consciousness, swallowing dysfunction, gastric stasis, increased intra-abdominal pressure due to ascites and ileus resulting from infection and electrolyte abnormalities. Those with cirrhosis are in a hyperdynamic and vasodilated state. Small decreases in arterial tone dramatically decrease circulating blood volume and precipitate hypotension. Cardiomyopathy with low normal ejection fraction, diastolic dysfunction, and delayed repolarization also play a role. Hepatic encephalopathy is also prevalent in cirrhotics. The activation of inflammatory mediators, such as cytokines, may enhance the effects of ammonia. Cognition may be impaired from disturbances of neurotransmission, injury to astrocytes, energy impairment, brain edema, loss of auto-regulation, and brain atrophy.

LITERATURE REVIEW

The mainstays of first-line treatment in patients with cirrhosis and ascites include (1) dietary sodium restriction (2000 mg per day [88 mmol per day]) and (2) oral diuretics. More stringent dietary sodium restriction can speed mobilization of ascites, but is not recommended because it is less palatable and may further worsen the malnutrition that is usually present in these patients. The usual diuretic regimen consists of single morning doses of oral spironolactone 100 mg and furosemide 40 mg. Starting with both drugs appears to be the preferred approach in achieving rapid natriuresis and maintaining normokalemia. An alternative approach would be to start with single-agent spironolactone. The doses of both oral diuretics can be increased simultaneously every 3 to 5 days (maintaining the 100 mg:40 mg ratio) if weight loss and natriuresis are inadequate. In general, this ratio maintains normokalemia. Usual maximum doses are 400 mg per day of spironolactone and 160 mg per day of furosemide. Hydrochlorothiazide has also been used to treat ascites. Hydrochlorothiazide can cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide; it should be used with extreme caution or avoided.

Oral midodrine 7.5 mg three times daily has been shown in a randomized trial to increase urine volume, urine sodium, mean arterial pressure, and survival. Midodrine can be added to diuretics to increase blood pressure and theoretically convert diuretic-resistant patients back to diuretic-sensitive.

When tense ascites is removed via large volume paracentesis, the fluid must be replaced. A meta-analysis of 17 trials involving 1225 patients demonstrated a reduction in mortality with an odds ratio of death of 0.64 (95% CI, 0.41-0.98) in patients receiving albumin replacement. Albumin was shown to be superior to other plasma expanders; the mean volume of ascitic fluid removed was 5.5-15.9 liters. Studies have variously infused between 5 and 10 g of albumin per liter of fluid removed; 6-8 g/L has been the most common dose.

HRS is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure. The diagnosis is essentially one of exclusion from other causes of renal failure. In 2007, the International Ascites Club modified the major criteria for the diagnosis of HRS and designated HRS into type 1 and type 2 HRS. Type 1 HRS is a rapidly progressive acute renal failure that frequently occurs in severe alcoholic hepatitis or in patients with end-stage cirrhosis following a septic insult such as spontaneous bacterial peritonitis. The most important trigger for the development of type 1 HRS is bacterial infection. Conventionally, type 1 HRS is only diagnosed when the serum creatinine increases more than 100% from baseline to a final level of greater than 2.5 mg/dl (221 µmol/L). Type 2

HRS occurs in patients with refractory ascites and there is a steady but moderate degree of functional renal failure, often with avid sodium retention. Patients with type 2 HRS may eventually develop type 1 HRS either spontaneously or following a precipitating infectious event.

The most effective treatment method currently available is the administration of vasoconstrictor drugs. Among the vasoconstrictors used, those that have been investigated more extensively are the vasopressin analogues particularly terlipressin. The rationale for the use of vasopressin analogues in HRS is to improve the markedly impaired circulatory function by causing a vasoconstriction of the extremely dilated splanchnic vascular bed and increasing arterial pressure with the goal of increasing renal perfusion. A large number of studies, randomized and non-randomized, have shown that terlipressin improves renal function in patients with type 1 HRS. Treatment is effective in 40–50% of patients. There is no standardized dose schedule for terlipressin administration because of the lack of dose-finding studies. Terlipressin is generally started at a dose of 1 mg/4–6 hrs and increased to a maximum of 2 mg/4–6 hrs if there is no reduction in serum creatinine of at least 25% compared to the baseline value at day 3 of therapy. Treatment is maintained until serum creatinine has decreased below 1.5 mg/dl (133 μmol/L). Response to therapy is generally characterized by a slowly progressive reduction in serum creatinine and an increase in arterial pressure, urine volume, and serum sodium concentration. Median time to response is 14 days and usually depends on pre-treatment serum creatinine, the time being shorter in patients with lower baseline serum creatinine. A serum bilirubin less than 10 mg/dl before treatment and an increase in mean arterial pressure of >5 mmHg at day 3 of treatment are associated with a high probability of response to therapy. Recurrence after withdrawal of therapy is uncommon and retreatment with terlipressin is generally effective. The most frequent side effects of treatment are cardiovascular or ischemic complications, which have been reported in an average of 12% of patients treated. It is important to emphasize that most studies excluded patients with known severe cardiovascular or ischemic conditions. Additionally, terlipressin was commonly given in combination with albumin (1 g/kg on day 1 followed by 40 g/day) to improve the efficacy of treatment on circulatory function. In the United States, as terlipressin is unavailable, we utilize vasopressin in lieu of terlipressin.

A European multicenter, randomized, controlled trial of terlipressin and albumin versus albumin alone in 46 patients with type 1 or type 2 HRS demonstrated an improvement in renal function, but no survival advantage at three months. The most recent meta-analysis of 8 studies involving 320 patients demonstrated ~50% efficacy and an odds ratio of 7.5 in reversing hepatorenal syndrome. Terlipressin is not available in the United States. Two randomized trials comparing norepinephrine to terlipressin, report equal efficacy in reversing type 1 or 2 hepatorenal syndrome in the former study and type 1 in the latter study.

A retrospective cohort study included patients who were admitted to the University of Colorado Hospital between January 1, 2000 and December 31, 2003. Recovery from HRS was defined as a decrease in the serum creatinine to a value <1.5 mg/dl. Forty-three patients were identified: eight received vasopressin, 16 received octreotide and 19 received both. Patients who received vasopressin alone or in combination with octreotide had significantly greater recovery rates than those receiving octreotide monotherapy (42% vs. 38% vs. 0%, respectively, $p<0.01$). The average time to response in serum creatinine was 7±2 days. The mean vasopressin dose was 0.23±0.19 U/min in patients demonstrating clinical response. Therapy with vasopressin was an independent predictor of recovery (odds ratio 6.4, 95% confidence interval 1.3–31.8). Patients who responded to therapy had significantly lower mortality (23% vs. 67%, $p<0.008$) and higher rates of liver transplantation (23% vs. 0%, $p<0.005$). No adverse effects related to vasopressin therapy were observed. When compared with octreotide, HRS patients treated with vasopressin had significantly higher recovery rates, improved survival and were more likely to receive a liver transplant.

Recent treatments for type 1 hepatorenal syndrome utilizing octreotide, midodrine, and albumin infusion have been found to be effective. In the initial study, 5 patients received 10 to 20 grams of intravenous albumin per day for 20 days, plus octreotide with a target dose of 200 micrograms subcutaneously 3 times per day, and midodrine titrated up to a maximum of 12.5 mg orally 3 times per day to achieve an increase in mean blood pressure of 15 mmHg. Results were superior to those of 8 patients treated with dopamine and albumin. This regimen can be administered outside of an intensive care unit and can even be given at home. A retrospective study involving 60 octreotide/midodrine/albumin-treated patients and 21 concurrent

nonrandomized albumin treated controls reported reduced mortality in the treatment group (43% vs. 71%, $p< 0.05$).

Transjugular intrahepatic portosystemic shunt (TIPS) has been reported to improve renal function in patients with type 1 HRS. However, the applicability of TIPS in this setting is very limited because many patients have contraindications to the use of TIPS. TIPS has also been shown to improve renal function and the control of ascites in patients with type 2 HRS. TIPS is effective in the management of refractory ascites, but is associated with a high risk of hepatic encephalopathy and studies have not been shown to convincingly improve survival compared to repeated large-volume paracentesis. TIPS should be considered in patients with very frequent requirement of large-volume paracentesis, or in those in whom paracentesis is ineffective (e.g. due to the presence of loculated ascites). This can be used as a bridge to transplant in the acute setting.

Liver transplantation is the treatment of choice for both type 1 and type 2 HRS, with survival rates of approximately 65% in type 1 HRS. The lower survival rate compared to patients with cirrhosis without HRS is due to the fact that renal failure is a major predictor of poor outcome after transplantation. Patients with type 1 HRS have a high mortality while on the waiting list and ideally should be given priority for transplantation. There seems to be no advantage in using combined liver–kidney transplantation versus liver transplantation alone in patients with HRS, with the possible exception of those patients who have been under prolonged renal support therapy (>12 weeks).

Non-absorbable disaccharides (lactulose or lactitol) are the mainstay of treatment of hepatic encephalopathy despite data showing no superiority of these drugs over placebo. They decrease ammonia levels in portal and systemic circulation. Oral daily doses of 40–60 g of lactulose or 30–50 g of lactitol have been advocated. Oral rifaximin (1100-1200mg/d), a non-absorbable derivative of rifamycin capable of modulating gut flora, is also effective in the treatment of acute hepatic encephalopathy with resolution rates similar or even higher than those observed with lactulose or lactitol.

Routine correction of coagulation abnormalities in the absence of active bleeding is not indicated. TEG, prothrombin time, complete blood count, and activated partial thromboplastin time are used to guide replacement therapy in cirrhosis. Isolated abnormalities in INR (in the absence of warfarin) with a normal partial thromboplastin time (PTT) and normal reaction time on a TEG do not require correction. Vitamin K 2 mg IV daily for 3-5 days should be administered to eliminate vitamin K deficiency as a source of coagulopathy. In the presence of bleeding, transfuse platelets to maintain a level of >50,000. Qualitative platelet dysfunction may be improved with desmopressin (DDAVP). Tranexamic acid is indicated when bleeding persists, despite correction of thrombocytopenia and clotting factors in the absence of disseminated coagulopathy. If PTT is excessively prolonged, use of protamine, even in the absence of heparin therapy, may be beneficial to counteract endogenous heparin-like compounds. Patients with cirrhosis are at risk for venous thromboembolism, even in the face of abnormal elevations of the INR or PTT.

Adrenal insufficiency in cirrhotic patients should be replaced at physiologic dosing. Routine use of steroids was not shown to be beneficial in a recent controlled trial.

REFERENCES

1. Runyon BA. Care of patients with ascites. N Engl J Med 1994; 330: 337-342.
2. Runyon BA. Ascites and spontaneous bacterial peritonitis. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th ed. Philadelphia: Saunders Elsevier, 2010:1517-41.
3. Gines P, Angeli P, Lenz K, Moller S, Moore K, Moreau R, Merkel C, et al. EASL clinical practice guideline on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. J Hepatol 2010; 53:397-417.
4. Singh V, Dhungana SP, Singh B, Vijayverghia R, Nain CK, Sharma N, Bhalla A, et al. Midodrine in patients with cirrhosis and refractory ascites: a randomized pilot study. J Hepatol 2012; 56:348-354.
5. Gines P, Tito L, Arroyo V, Planas R, Panes J, Viver J, Torres M, et al. Randomized study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988; 94:1493-1502.
6. Gines A, Fernandez-Esparrach G, Monescillo A, Vola C, Domenech E, Abecasis R, Angeli P, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996; 111:1002-1010.
7. Bernardi M, Carceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012; 55:1172-1181.
8. Angeli P, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, Amodio P, et al. Reversal of type I hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999; 29:1690-1697.
9. Esrailian E, Pantangco ER, Kyulo NL, Hu K-Q, Runyon BA. Octreotide/ midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. Dig Dis Sci 2007; 52:742-748.
10. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). Am J Transplant 2008; 8:2243-2251.
11. Tyree H. Kiser, Douglas N. Fish, Marilee D. Obritsch, Rose Jung, Robert MacLaren, and Chirag R. Parikh. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study Nephrol Dial Transplant 2005; 20 (9):1813-1820.
12. Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ 2010; 182:1971-1977.

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Anthony Gielow, DO
Editor: Michael L. Cheatham, MD, FACS, FCCM
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Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net