What I Wish I Had Known About Cirrhotics When I Was a Resident
**Introduction**

I remember quite clearly the feeling of dread that came over me, as a young resident, when I was told I would be treating a cirrhotic patient. I spent much of my residency feeling quite clueless on the management of complications associated with cirrhosis. Residency is a unique time during which one is bombarded by information so fast it is hard to assimilate, and, at the same time, one often doesn’t know where to begin. I often felt overwhelmed when I tried to read up on many of the topics I have covered in this handbook, especially considering the little bit of clinical experience I had with these patients. My aim for this handbook is to cover the basics of the major complications of portal hypertension. Obviously, this handbook is only an introduction and should not take the place of more definitive reading. My hope is that after reading this handbook, which shouldn’t take too long, residents will feel less overwhelmed than I did and have an easy, quick resource when questions come up. Good luck!

On a separate note, I’d like to thank all the hepatologists, fellows, residents, and my sister for reading this handbook and giving me their suggestions for improvement.

Aliya G. Hasan  
January 2007

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Sakai II, Mendler MH, Runyon BA. The left lower quadrant is the best site for paracentesis: an ultrasound evaluation. Hepatology 2002;36:525A.


UpToDate

References:


Brown WR. Gastroenterology for dummies. UCHSC GI website 2006.


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Ascites

Ascites is the most common of the three major complications of cirrhosis and has developed in up to 50% of patients with compensated cirrhosis during a ten-year observation. Unfortunately for those patients, the development of ascites can portend a poor prognosis, as 50% of these patients will die within two years. As a result, the development of ascites usually prompts referral for liver transplant evaluation.

Although most patients with ascites have chronic liver disease, not all do. In fact, about 15% of patients will turn out to have a non-hepatic cause. An accurate diagnosis of the etiology is important, as the diagnosis will have implications for eventual treatment. The best method proven by prospective study for diagnosis is to calculate the serum-ascites albumin gradient also known as the SAAG.

**SAAG**

\[
\text{SAAG} = \text{Serum Albumin} - \text{Ascitic Fluid Albumin}
\]

(These values should be obtained on the same day.)

If the SAAG is greater than or equal to 1.1 g/dL, the patient has portal hypertension with approximately 97% accuracy. Patients with multiple etiologies for ascites, including portal hypertension, can also have a SAAG greater than or equal to 1.1. Generally only about 5% of patients will fall into this category.

<table>
<thead>
<tr>
<th>High gradient (&gt; 1.1 g/dl)</th>
<th>Low gradient (&lt;1.1 g/dl)</th>
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<tbody>
<tr>
<td>Cirrhosis</td>
<td>Peritoneal carcinomatosis</td>
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<tr>
<td>Alcoholic hepatitis</td>
<td>Tuberculous peritonitis</td>
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<tr>
<td>Cardiac ascites</td>
<td>Pancreatic ascites</td>
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<tr>
<td>&quot;Mixed&quot; ascites</td>
<td>Bowel obstruction or infarct</td>
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<tr>
<td>Fulminant hepatic failure</td>
<td>Biliary ascites</td>
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<td>Budd-Chiari syndrome</td>
<td>Nephrotic syndrome</td>
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<tr>
<td>Portal vein thrombosis</td>
<td>Postoperative lymphatic leak</td>
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<tr>
<td>Veno-occlusive disease</td>
<td>Serositis (connective tissue diseases)</td>
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<tr>
<td>Myxedema</td>
<td></td>
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<tr>
<td>Fatty liver of pregnancy</td>
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Pain Medications in Cirrhosis

Management of pain in patients with cirrhosis can be problematic as commonly prescribed medications can cause serious, harmful effects. Typically as the patient’s liver disease worsens, the chance of a side effect being dangerous increases due to altered pharmacokinetics and hemodynamic changes. A more complete review of this topic can be found on UpToDate. The following are general recommendations regarding use of common analgesic and anti-inflammatory agents in patients with cirrhosis.

**Acetaminophen** – Safe up to a maximum of 2 grams per day, so half the recommended dosage.

**NSAIDs (including aspirin)** – Avoid. These medications are associated with an increased risk of variceal hemorrhage, impaired renal function, and development of diuretic resistant ascites.

**COX-2 Inhibitors** – Avoid. Although experience is limited, it is felt that there can be deleterious effects associated with these medications as is the case with NSAIDs.

**Ultram** – Thought to be safe for use, although consider reduced dosage and prolonged intervals.

**Opioids**

Generally these medications are metabolized through hepatic oxidation and glucuronidation. Clearance depends on plasma protein binding, hepatic blood flow, and hepatic enzyme capacity. Since oxidative enzyme pathways and clearance are impaired in patients with cirrhosis, accumulation of toxic metabolites ensues.

**Morphine, Hydromorphone, and Oxycodone** – Use with caution at reduced doses and prolonged intervals of dosing.

**Fentanyl** – Evidence suggests that the pharmacokinetics of fentanyl are similar when comparing healthy patients to those with mild cirrhosis, so probably safe in patients with modest hepatic dysfunction.

**Methadone** – Evidence also suggests that there are similar pharmacokinetic profiles whether the patient is healthy or has mild to moderate cirrhosis. Methadone appears to be safe in patients with cirrhosis.
- Extrahepatic malignancy (excluding some skin cancers)
- Extensive hepatocellular carcinoma or with macrovascular or lymph node invasion *
- Cholangiocarcinoma *
- Uncontrolled systemic sepsis
- Extensive portal vein and mesenteric vein thrombosis
- Active alcohol or drug use (Patients should be abstinent at least 6 months)
- Non-compliance
- Unacceptable risks for recidivism from drugs or alcohol
- Severe, uncontrolled psychiatric disease
- AIDS (HIV) *
- No insurance

Relative contraindications
- Moderate pulmonary hypertension (mean PAP between 35 and 50 mmHg) *
- Severe hepatopulmonary syndrome with PaO₂ of ≤ 50 mmHg
- Severe obesity (body mass index ≥ 35)
- Poor social support including homelessness
- Advanced age (≥ 70)

* Liver transplant has been performed in some centers under an experimental protocol.

Transplant for Hepatocellular Carcinoma (HCC)

The current best treatment for patients with HCC and cirrhosis is liver transplant, but it is not necessarily a viable treatment for all patients. Since HCC recurrence is strongly correlated with tumor size, number of nodules, and presence of vascular invasion, the right patients have to be selected for transplant in order to have a survival advantage. In patients who meet these criteria their 5-year mortality is equivalent to that for liver transplant. These criteria are known as the Milan criteria:

1. Single lesion ≤ 5 cm
2. ≤ 3 lesions each ≤ 3 cm
3. No radiographic evidence of extra-hepatic disease.

Treatment

The International Ascites Club has defined uncomplicated ascites as those which are not infected or associated with the development of hepatorenal syndrome. Grade 1 ascites is defined as mild ascites that is only detectable by ultrasound. Grade 2 is considered to be moderate sized ascites and is manifested by moderate symmetrical distention of the abdomen. Grade 3 is large volume ascites with marked abdominal distention.

Grade 1 ascites does not require specific treatment, except that the patient should be followed clinically and advised to lower their sodium intake.

The mainstays for treatment of grade 2 ascites are:
1. Low sodium diet, meaning 2000 mg per day (88 mmol)
2. Oral diuretics.

Education regarding sodium intake is probably the single best thing we as housestaff can re-enforce to the patients. Abstaining from salt at the lunch or dinner table is not enough. Patients have to train themselves to look at the salt content of the foods they are eating. The patients need to understand that fluid loss is directly related to sodium balance. The more salt ingested, the more water retained, since fluid passively follows sodium. So, in order to lose fluid, or the weight from that excess fluid, sodium restriction is the key.

For effective treatment the urinary excretion of sodium should be greater than 78 mmol per day (88 mmol intake − 10 mmol nonurinary excretion). Perhaps the easiest way to objectively assess compliance with treatment is to do a random, spot urine and potassium concentration. A random spot urine sodium concentration that is greater than the potassium concentration correlates with a 24-hour sodium excretion greater than 78 mmol per day with approximately 90% accuracy. 24-hour urine sodium measurement is another albeit more cumbersome method to assess compliance. If the urine sodium/potassium ratio is greater than 1, or the 24-hour urine sodium is greater than 78 mmol per day, but the patient is not losing weight, then the patient’s compliance with the low salt diet needs to be examined. Patients who are excreting more than 78 mmol per day of sodium in the urine without losing weight are usually consuming more than the 88 mmol per day sodium recommendation.

As far as diuretics, the usual regime consists of single morning doses (to maximize compliance) of oral spironolactone and furosemide. Actually, spironolactone has been shown to be the stronger single-agent diuretic but, due to hyperkalemia difficult to use alone. The starting doses usually are 100 mg of spironolactone and 40 mg of furosemide. This 100:40 ratio generally maintains normokalemia. Both diuretics can be increased simultaneously.
every 3 to 5 days until a good diuresis is achieved. Usually each medication is doubled until the maximum dose is achieved, 400 mg for spironolactone and 160 mg for furosemide. Obviously the ratio of these medications can be adjusted based on the patient’s potassium level. Of note, some patients on spironolactone will develop tender gynecomastia. In these patients, the spironolactone can be substituted for amiloride, 10-40 mg per day. Amiloride has been shown to be less effective than spironolactone.

In patients with peripheral edema, although there is no limit to the daily weight loss that can be achieved through diuresis, the International Ascites Club recommends diuresis of no more than 1 kg/day. Once the peripheral edema has resolved, only about 0.5 kg is a reasonable daily maximum. This difference is because patients who only have ascites have to mobilize fluid from peritoneal capillaries. The max rate that this mobilization can occur is 300-500 mL/day. Diuresis at a rapid rate will lead to plasma volume depletion and azotemia. In patients with large volume ascites and minimal peripheral edema, large volume paracentesis is probably the best route to pursue.

The few caveats to diuretic treatment are encephalopathy, serum sodium less than 120 despite fluid restriction, or serum creatinine greater than 2.0. If any of these situations develop, then diuretics should be stopped, and the clinical picture should be re-assessed. Eventually, the patient may need to go on to second-line options for treatment.

The treatment for grade 3 ascites is similar to that of grade 2 except that paracentesis is a necessary adjunct to remove the majority of fluid, since diuretics usually are not enough. See the Paracentesis section for more information regarding this procedure.

Re refractory ascites

Refractory ascites is defined as fluid overload that is unresponsive to sodium restriction and high dose diuretic treatment, or recurs rapidly after therapeutic paracentesis. Less than 10% of patients should fall into this group. Options for treatment at this point include: serial therapeutic paracenteses, liver transplant, and transjugular intrahepatic portosystemic stent-shunt (TIPS). Peritoneovenous shunt was a therapeutic option in the past, but, with the advent of TIPS and the complications associated with the surgery, peritoneovenous shunt has basically been abandoned as a treatment option.

Another very good treatment option for patients with refractory ascites, who are not candidates for the TIPS procedure, is the use of weekly albumin infusions followed by intravenous lasix. Trotter et al have reported on the UCHSC experience with this treatment, and they found that recurrent, subjective criteria associated with the CTP score allowed room for abuse, so a better scoring system was sought. In February 2002 organ allocation shifted to use the Model for End-Stage Liver Disease (MELD), which only included objective data.

\[
\text{MELD} = 3.78 \times \log_e (\text{bilirubin [mg/dL]}) + 11.2 \times \log_e (\text{INR}) + 9.57 \times \log_e (\text{creatinine [mg/dL]}) + 6.4.
\]

The MELD was originally developed to assess short-term prognosis in patients undergoing TIPS procedures. Subsequent studies of this model demonstrated that it was an effective tool to determine prognosis in patients with cirrhosis.

3-month mortality according to MELD score:

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>≤ 9</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>≥ 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>4%</td>
<td>27%</td>
<td>76%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Outpatient</td>
<td>2%</td>
<td>6%</td>
<td>50%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

The higher a patient’s MELD score, the higher they go up on the transplant list. Depending on how high the score, it is recalculated at set intervals—meaning the higher scores are recalculated more often.

Transplant Evaluation

Once it is determined that a patient will benefit from liver transplantation, a multi-disciplinary team starts the evaluation process. This evaluation addresses the following fundamental questions:

1. Can the patient survive the operation and the immediate postoperative period?
2. Can the patient be expected to comply with the complex medical regimen required after liver transplant?
3. Does the patient have other co-morbid conditions that could so severely compromise graft or patient survival that transplantation would be futile and an inappropriate use of a scarce donor organ?

Careful medical, surgical, and psychosocial assessment ensues in order to answer these questions.

Contraindications to Liver Transplantation

Absolute contraindications

- Severe, irreversible co-morbid medical illness that adversely impact short-term life expectancy
- Severe pulmonary hypertension (mean PAP ≥ 50 mmHg) *
Liver Transplantation

Liver transplantation is usually considered when a patient with cirrhosis develops a complication of portal hypertension. When these complications occur, the patient goes from having compensated disease to **decompensated cirrhosis**. This decompensation leads to significantly impaired survival, hence the need for transplant evaluation. How sick the patient is versus the risks associated with transplant surgery and immunosuppression needs to be evaluated and balanced, so that transplant only proceeds in patients who are felt to benefit from having a new liver. According to the United Network for Organ Sharing (UNOS), only patients with an estimated 90% or less chance of 1-year survival should be listed for transplant.

Matching of an appropriate donor organ with a recipient only requires compatibility of the ABO blood type, and not human leukocyte antigen (HLA) tissue type. Most transplants use a whole liver from a deceased donor which is placed in the orthotopic position (meaning the normal anatomic location), hence the term orthotopic liver transplantation (OTL). In living donor transplantation, the right lobe of the donor liver is taken out and transplanted into the recipient. In both the donor and the recipient, there is a rapid regeneration of the liver with full size being regained in 6 to 8 weeks.

In the past the Child-Turcotte-Pugh (CTP) score was calculated to risk-stratify patients before transplant. The CTP classification was originally designed to stratify the risk of portacaval shunt surgery in patients with cirrhosis and variceal bleeding.

**Child-Pugh Classification of Severity of Liver Disease**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Grade</th>
<th>Disease Classification</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>Well-compensated disease</td>
<td>100%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>Significant functional compromise</td>
<td>80%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>Decompensated disease</td>
<td>45%</td>
</tr>
</tbody>
</table>

weekly albumin infusions resulted in significant loss of edema and ascites as measured by loss of body weight.

**Inpatient Admissions for Fluid Overload**

There will be patients admitted directly from clinic or home to the UCHSC hepatology service for inpatient diuresis due to volume overload. From a diagnostic point of view, it is important to understand why these patients became so fluid overloaded; were they non-compliant with diet or meds, do they have a TIPS which is no longer patent, or is there some other reason?

In this setting the mainstays for treatment of these patients tend to be twice daily intravenous albumin infusion (usually if their serum albumin is less than 3.5), followed by intravenous lasix (usually starting at 40 mg). The caveats for diuretic treatment are the same as discussed in the treatment section. Large volume paracentesis is also a useful adjunct. Obviously the patient’s fluid status is closely watched through daily weights, I/O recording, and physical exam. Since these patients are in the hospital, their status is re-assessed daily, along with corresponding adjustments to medications. In this setting, patients tend to have a much more dramatic response to treatment than they do in the outpatient setting.

Do look to the fellow and attending on service for more guidance in regards to these admissions, especially as there may be subtle differences from patient to patient.
Hyponatremia

Hyponatremia seen in patients with cirrhosis is due to an effective circulating volume depletion leading to elevation of ADH levels. This condition is chronic, and is not one that needs to be treated aggressively.

The mainstay of treatment is fluid restriction, which is not necessary in most patients. In fact, attempts to rapidly correct hyponatremia with hypertonic saline can lead to more complications than the hyponatremia itself. There is no data supported threshold for initiating fluid restriction, but a serum sodium less than 120-125 seems to be a reasonable time to start fluid restriction. Generally cirrhotic patients do not usually manifest symptoms until their sodium level is below 110 or they have had a rapid decline in sodium.

In the inpatient setting, if hyponatremia becomes a problem, rather than fluid restriction, treatment with intravenous albumin, normal saline, and low dose lasix under careful observation can resolve the hyponatremia more quickly. Look to the fellow and attending on service for more guidance in these patients.

Bottom line: not all patients with cirrhosis need to be fluid restricted – only those with serum sodium levels below 120-125. Fluid should be restricted to 1.5 liters per day, if indicated.

of choice at UCHSC as it is a preferential splanchnic vasoconstrictor. It can correct hemodynamics in patients with advanced cirrhosis by increasing the mean arterial pressure, decreasing renin and norepinephrine, increasing renal blood flow, increasing GFR, and increasing urine sodium excretion. There is a delay of several days between improvement in circulatory function and the increase in GFR, probably about 10 days. Of note, once approved by the Federal Drug Administration (FDA), terlipressin, an analog of vasopressin, will likely become the treatment of choice.

In order to receive vasopressin, patients have to be in either the step-down unit or the intensive care unit (ICU) because often the infusion has to be titrated, and the patients need to be closely monitored while on it. Complications of vasopressin include: cardiac arrest or arrhythmia, myocardial infarction, mesenteric ischemia, and hyponatremia. Also of concern is the severe localized tissue necrosis which can ensue, if there is extravasation of the medication at the IV site. Although vasopressin can be given peripherally, given the length of the time the patient is on it, and the concern for tissue necrosis, it is probably best given centrally.

Others advocate treatment with midrodine (alpha-adrenergic agonist), octreotide (suppresses glucagon), and IV albumin. At UCHSC, midrodine and octreotide are generally not used because the evidence for their benefit is felt to be extremely weak by both the hepatologists and nephrologists.

Prevention of HRS

HRS can be prevented in specific clinical settings, namely SBP and alcoholic hepatitis. Sort et al found that by giving IV albumin along with antibiotics for SBP markedly reduced the incidence of impairment in circulatory function and the occurrence of type 1 HRS (10% in treatment group, 33% control group). Akriviadis et al found that administration of pentoxyfilline (tumor necrosis factor (TNF) inhibitor) to patients with alcoholic hepatitis reduced the occurrence of HRS (8% in treatment group, 35% in placebo) and hospital mortality (24% vs 46%).
and anti-diuretic hormone (ADH), along with very low GFR (<40). There is data to suggest that HRS also develops when the hyperdynamic circulation cannot be maintained because of a decrease in cardiac output.

Bottom line: HRS is a functional renal impairment. It is important to remember that the kidneys themselves are normal, and the disease generally disappears after transplant.

**Diagnosis**

The first step in diagnosis is the demonstration of a decreased GFR. The second step is the differentiation of HRS from other types of renal failure.

Major Diagnostic Criteria according to the International Ascites Club:
1. Hepatic failure and portal HTN
2. Creatinine > 1.5 or GFR < 40
3. No shock, ongoing bacterial infection, nephrotoxic agents, or fluid losses (diarrhea)
4. No improvement after diuretic withdrawal and 1 g/kg of albumin infusion
5. Proteinuria < 500 with normal renal ultrasound

**Types of HRS**

Type 1 HRS is characterized by a severe and rapid progressive renal failure, defined as doubling of serum creatinine reaching a level > 2.5 in less than 2 weeks. Although it can arise spontaneously, it usually occurs in close relationship to a precipitating event like a severe bacterial infection, GI bleed, major surgery, or acute hepatitis superimposed on the cirrhosis. The underlying mechanism for the development of type 1 HRS is more likely due to impairment of circulatory function leading to renal ischemia. After onset, type 1 HRS has the poorest prognosis with a median survival of about 2 weeks.

Type 2 HRS on the other hand is characterized by a moderate and steady decrease in renal function (creatinine < 2.5). The dominant clinical feature is severe ascites with poor or no response to diuretics. A decrease in cardiac function probably plays more of a role in the mechanism of type 2 HRS. Not surprisingly these patients are especially predisposed to developing type 1 HRS. The median survival is about 6 months.

**Treatment**

The treatment of choice is liver transplant. While waiting for transplant, the key to treatment is decreasing the splanchnic vasodilation and volume expansion. Vasopressin, an analog of ADH, is currently the treatment of choice.

**Paracentesis**

The indications for paracentesis are: (1) new onset ascites; (2) at every hospital admission; (3) clinical deterioration (fever, abdominal pain or tenderness, mental status change, ileus, or hypotension); (4) lab abnormalities that may indicate the presence of an infection (high WBC, acidosis, worsening renal function); and (5) GI bleed. Basically, there should be a low threshold when it comes to analyzing ascitic fluid.

In my experience, many patients don’t have paracenteses performed because of concerns either regarding complications or the cumbersome nature of the procedure, which is often performed in the middle of the night. Actually, paracentesis is quite safe. Grabau et al reported on 1100 large volume paracenteses performed by their GI endoscopy assistants. The mean INR was 1.7 with a range of 0.9-8.7, and the mean platelet count was 50,400 with a range of 19,000-341,000. The mean volume of ascitic fluid removed was 8.7 +/- 2.8 L. There were no significant procedure related complications, even in the patients with high INR or low platelets. Looking more specifically at bleeding, Pache et al reviewed all cases of severe hemorrhage after paracentesis admitted to their institution. They found 9 cases among 4729 procedures, representing 0.19% of all procedures with a death rate of 0.016%. In their study, bleeding was not related to operator experience, elevated INR, or low platelets; it occurred in patients who had higher MELD or Child-Pugh scores. They also found some degree of renal failure in all but one patient. Bottom line: the risk of severe hemorrhage is low and occurs in patients with severe liver failure and often those with pre-existing renal dysfunction. Other complications, like bowel entry by the needle, occur, but they are quite unusual – enough so that it should not deter the performance of the procedure.

If coagulopathy is present, many physicians feel better if they give fresh frozen plasma (FFP) or platelets prior to paracentesis. It is important to know that this practice is not data-supported and is not recommended. Overall, it is felt that the risks and costs of prophylactic transfusions exceed any benefit. The only situation where coagulopathy should trigger concern is in patients with clinically evident fibrinolysis or clinically evident disseminated intravascular coagulation. There is no data to support specific cutoffs for coagulation parameters, so in these cases clinical judgment should be exercised.

The most recent guideline for how paracentesis should be performed is described by Sakai et al. Briefly, they recommend the left lower quadrant, 2 finger breadths cephalad and 2 finger breadths medial to the anterior superior iliac spine, because it has been shown to be thinner and with a larger pool of fluid than the midline. If it is difficult to ascertain where fluid is, then ultrasound can be used. Of note, some hepatologists prefer the right side over
the left, so that enlarged spleens can be avoided; but procedures can be safely performed on either side.

Finally, don’t forget that a trocar doesn’t have to be used to perform a paracentesis. You can use a 19-gauge needle with a syringe to pull off a small amount of fluid for diagnostic purposes only. Since it is one needle stick, you can even talk to the patient about skipping the lidocaine step, as that would make it two needle sticks. Even if you are in a hurry or pressed for time, doing the procedure this way takes very little time (even with the lidocaine step).

How Much to Take Off?

To answer this question, Tito et al performed a “total paracentesis,” meaning they took off a mean of about 10 L in one session with intravenous albumin infusion on 38 cirrhotic patients. They had no patients develop renal impairment. Other complications were similar to those reported in patients treated with repeated 4-6 L/day taps. They concluded that total paracentesis with intravenous albumin infusion could be safely performed in cirrhotic patients with tense ascites.

That said, there are patients who do develop renal impairment with total paracentesis. The best answer to the question is that if the patient is having their first ever paracentesis for tense ascites, don’t take off more than 4-6 L and see how they tolerate this minimum. If there are no complications, then more can probably be safely removed the next time.

Colloid Replacement

As mentioned in the above study, albumin infusion is often given with large volume paracenteses, but this issue is a controversial one. Until the question is definitively answered, the AASLD guidelines state, “It is reasonable although not mandatory to give it [albumin] for paracenteses greater than 5 L…For large-volume paracenteses, an albumin infusion of 8 to 10 g/L of fluid removed can be considered.”

On the Hepatology service, we generally give albumin, 50 g of 25% solution, if more that 5 L is to be removed.

Hepatorenal Syndrome (HRS)

HRS refers to the development of acute renal failure in patients who usually have advanced liver disease due to cirrhosis, severe alcoholic hepatitis, and fulminant hepatic failure. There are many aspects of HRS which are still poorly understood. I think in order to understand how to treat HRS, it is important to understand what is thought to be the pathophysiology behind it.

Pathophysiology

As portal pressure increases, splanchnic arterial vasodilation is noted. This vasodilation increases inflow of blood into the portal venous system, and allows the portal pressure to remain elevated despite the development of a collateral circulation. A compensatory mechanism to the splanchnic arterial vasodilation is the hyperdynamic circulation.

This hyperdynamic circulation is characterized by: increased plasma volume, increased cardiac index, increased heart rate, reduced arterial pressure, reduced peripheral vascular resistance, and high cardiac output due to low cardiac preload and increased heart rate. Reduction in central blood volume stimulates volume receptors in the right atria, pulmonary circulation, and pressure receptors in the aorta and cardiac sinus leading to a reflex stimulation of the sympathetic nervous system and renin-angiotensin system (RAS).

Renal dysfunction in patients with cirrhosis begins with the reduced ability to excrete sodium. As the disease progresses the impairment in sodium metabolism increases, and a critical point is achieved at which patients are unable to excrete as much sodium as that taken in. This retention of sodium leads to ascites.

As the RAS and sympathetic nervous systems are activated to maintain arterial pressure, normal or near normal renal function is critically dependent on an increased renal production of prostaglandins. These prostaglandins act as vasodilators antagonizing the vasoconstrictor effects of the RAS and the sympathetic nervous system. NSAIDs given at this stage can mimic HRS as they reduce the amount of prostaglandin in the body.

The development of HRS is heralded by the impairment in glomerular filtration rate (GFR) due to decreased renal perfusion. This decreased perfusion is secondary to renal vasoconstriction resulting from an imbalance between the activity of systemic vasoconstriction and the renal production of vasodilators. Once HRS develops, it is characterized by low arterial pressure, marked increase in plasma levels of renin, norepinephrine,
Chronic Encephalopathy

- Avoidance and prevention of precipitating factors, including the institution of prophylactic measures.
- **Nutrition.** Improve protein intake by feeding dairy products and vegetable-based diets. Oral branched-chain amino acids can be considered for individuals intolerant of all protein. Per UpToDate protein intake should be limited (to 70 g/day), but not restricted as it will lead to negative nitrogen balance.
- **Lactulose.** Dosing aims at two to three soft bowel movements per day. Antibiotics are reserved for patients who respond poorly to disaccharides, or who do not exhibit diarrhea or acidification of the stool. Chronic antibiotic use (neomycin, metronidazole) requires careful renal, neurological, and/or otological monitoring. (Note – rifaximin is a good alternative)
- Refer for liver transplantation in appropriate candidates.

### Ascitic Fluid Analysis

According to AASLD practice guidelines:

<table>
<thead>
<tr>
<th>Why Paracentesis is Being Done</th>
<th>What to Send For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated cirrhotic ascites</td>
<td>Cell count and diff, albumin, and total protein</td>
</tr>
<tr>
<td>Suspected ascitic fluid infection</td>
<td>Cell count and diff, albumin, and bacterial culture in blood culture bottles (10mL fluid/bottle)</td>
</tr>
<tr>
<td>Serial outpatient therapeutic paracentesis</td>
<td>Can do cell count and diff (rare to find it positive)</td>
</tr>
</tbody>
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Other studies performed should be based on the clinical picture, or if there are abnormalities in the initial testing which would warrant further study.
Spontaneous Bacterial Peritonitis (SBP)

SBP is an ascitic fluid infection without evidence of an intra-abdominal surgically treatable source. It tends to occur in patients with advanced cirrhosis in the setting of large volume ascites. An elevated ascitic fluid absolute PMN (polymorphonuclear leukocyte) count ≥ 250 cells/mm³ +/- a positive ascitic fluid bacterial culture makes the diagnosis, or a total white blood cell (WBC) ≥ 500.

When to Test for SBP

The diagnosis of SBP should be evaluated in all patients who develop clinical signs of infection like: abdominal pain/tenderness; fever of 100°F or more; hypothermia; encephalopathy; renal failure; acidosis; or peripheral leukocytosis. All patients with ascites who are admitted into the hospital should be tested for SBP, as Dr. Runyon has found that up to 13% of these patients can be infected without any overt clinical signs. Testing should be repeated in these patients if they have any clinical change during the course of their hospitalization. Such changes could be due to infection.

Treatment

If the ascitic fluid PMN count suggests SBP, then the patient should be empirically treated with antibiotics. Treatment should never be delayed to see what the culture grows out, because such a delay in treatment could have a disastrous outcome. Even if the PMN count is negative, if a patient has convincing signs or symptoms of infection, they should be treated. Broad spectrum therapy is warranted until bacterial cultures can help narrow the antibiotic. AASLD practice guidelines recommend cefotaxime 2g IV every 8 hours or similar third-generation cephalosporin, as it covers the three most common isolates: *Escherichia coli*, *Klebsiella pneumoniae*, and *pneumococcus*. The guidelines also suggest oral ofloxacin 400 mg twice a day can be considered in patients who aren’t very sick, meaning the patients have no: vomiting, shock, grade II or higher hepatic encephalopathy, or serum creatinine greater than 3 mg/dL. Patients should be treated for 5 days.

Follow-up ascitic fluid analysis is unnecessary in all patients with SBP. If they have a typical clinical course with a good clinical response to treatment, then repeat paracentesis is not necessary. If there is anything atypical about the clinical picture, then repeat paracentesis should be performed. Generally, if the repeat paracentesis is positive with a PMN count greater than the initial one, the possibility of secondary peritonitis should be investigated.

Data has emerged that rifaximin, which is a non-absorbed derivative of rifamycin, is a good alternative as it is has a favorable side-effect profile. In a recent review, Festi et al noted that rifaximin is a useful alternative to lactulose for the treatment of grade I-III encephalopathy, because it proved itself to be very effective both in reducing blood ammonia and improving clinical status in patients. Due to its lack of absorption, it is remarkably safe for long term use. What exact role rifaximin should play in the treatment of hepatic encephalopathy has not been established; but, for now, it is an effective, safe treatment for both acute exacerbation of and chronic encephalopathy. The dose of rifaximin is 400 mg po TID.

The Practice Parameters Committee of the American College of Gastroenterology has published the following guidelines for treatment of hepatic encephalopathy in patients with cirrhosis:

**Acute Encephalopathy**

- Identification and correction of the precipitating factor is the most important measure.
- Avoid sedatives whenever possible.
- If a patient is in deep encephalopathy, intubation should be considered.
- **Nutrition.** In case of deep encephalopathy, oral intake is withheld for 24–48 h and i.v. glucose is provided until improvement. Enteral nutrition can be started if the patient appears unable to eat after this period. Protein intake begins at a dose of 0.5 g/kg/day, with progressive increase to 1–1.5 g/kg/day.
- **Lactulose** orally, via enema, or nasogastric tube in deep encephalopathy is the first line treatment. Orally it can be given every hour until stool evacuation appears.
- Lactulose can be replaced by oral neomycin. (Note – Many feel that neomycin is not very effective in the acute setting and are concerned about its toxicity, so it is not recommended for use in UpToDate. At UCHSC, we use rifaximin instead.)
- **Flumazenil** may be used in selected cases of suspected benzodiazepine use.
Treatment

Treatment of the precipitating cause typically leads to a prompt improvement of the encephalopathy, which again underscores the importance of looking for the precipitating event.

Otherwise, treatment is aimed at either reducing or inhibiting intestinal ammonia production or increasing the removal of ammonia. Treatment strategies include: diet modification to decrease the amount of protein being taken in, synthetic non-absorbable disaccharides like lactulose, and antibiotics with activity against urease-producing bacteria like neomycin or rifaximin.

Although dietary protein restriction has been recognized as an effective treatment, it can be problematic because it can lead to a negative nitrogen balance. Due to their increased catabolic rate, patients with cirrhosis require at least 0.8 to 1.0 g/kg of protein daily to maintain normal nitrogen balance. Supplementation with vegetable rather than animal protein can be suggested, as it has been shown to improve nitrogen balance without precipitating or worsening encephalopathy.

Lactulose reduces the plasma ammonia concentration by its cathartic effects, as well as by lowering the colonic pH when it is catabolized by bacterial flora to short chain fatty acids. This change in pH creates a hostile environment for the urease-producing intestinal bacteria; and results in a net movement of ammonia from the blood into the bowel lumen, because the acid environment favors the formation of the non-absorbable NH4+ from NH3. Although the therapeutic trials of lactulose are not of the best quality and analysis of the literature regarding it may question its effectiveness, it is still considered to be a valuable treatment and represents the current mainstay of treatment. It should be given 30-45 mL po TID, titrated to 2-3 stools daily. It can also be given as a 300cc retention enema every 4-6 hours. Approximately 70-80% of patients will improve on lactulose. It is well tolerated, but side effects can include abdominal cramping and flatulence.

Antibiotics with activity against urease-producing bacteria, like neomycin or metronidazole, reduce the production of intestinal ammonia. The efficacy of neomycin is thought to be similar to that of lactulose for chronic treatment of encephalopathy, but since a small percentage of the drug is absorbed systemically, side effects like ototoxicity and nephrotoxicity can

Another important adjuvant to antibiotics is thought to be albumin. Sort et al conducted a controlled trial where patients with SBP were randomized to receive cefotaxime alone versus cefotaxime plus 1.5 g albumin per kg body weight within 6 hours of enrollment and 1.0 g/kg on day 3. The albumin group had a decrease in renal impairment from 33% (control group) to 10%, and more importantly a decrease in mortality from 29% (control group) to 10%. So patients with SBP should also receive 1.5 g/kg albumin within 6 hours of diagnosis and 1.0 g/kg on day 3.

Secondary Bacterial Peritonitis

Secondary peritonitis is generally due to either a free perforation of a viscus or a loculated abscess in the absence of a perforation. Clinically, it can be difficult to distinguish between spontaneous and secondary causes; so, characteristics of the ascitic fluid and the patient’s response to the treatment can aid in the diagnosis. The ascitic fluid in the case of perforation would reveal: PMN count ≥ 250 cells/mm³, multiple organisms on gram stain and culture, and at least 2 of the following – total protein > 1 g/dL, lactate dehydrogenase > upper limit normal for serum, and glucose < 50 mg/dL. As far as peritonitis secondary to an abscess, total protein, lactate dehydrogenase, and glucose are only 50% sensitive. In these patients, a PMN count that increases after 48 hours of treatment helps in making the diagnosis.

Obviously, patients who are thought to have secondary peritonitis should undergo appropriate imaging and evaluation by a surgeon.

Prophylaxis

Clearly, long term antibiotics are problematic when one considers the risk of resistance. There are certain scenarios where prophylaxis is felt to be beneficial – patients who have had one or more episodes of SBP, patients who come in with a variceal bleed, and hospitalized patients who have an ascitic total protein < 1 g/dL. There is also evidence that patients with an ascitic total protein ≤ 1 g/dL or bilirubin > 2.5 mg/dL benefit from continuous prophylaxis.

In the case of a variceal hemorrhage, it is recommended to give either 400 mg norfloxacin po twice daily or trimethoprim-sulfamethoxazole (one double-strength tablet twice daily) for seven days total. Patients who have already had an episode of SBP or are considered high risk should be prophylaxed with norfloxacin 400 mg po daily or one tablet of double-strength trimethoprim-sulfamethoxazole daily. The same dosing can be used for hospitalized patients with an ascitic fluid protein level < 1; the drug should be discontinued at discharge. Weekly or five times per week dosing is not recommended by the AASLD guidelines due to concerns that intermittent dosing may select resistant flora more rapidly.
Varices

In the setting of portal hypertension, varices develop in order to decompress the hypertensive portal vein and return blood to the systemic circulation. The average lifetime risk for a variceal bleed is about 30% in cirrhotics who have not bled before. Each bleeding episode can be associated with a mortality risk between 30-50%.

Screening for Esophageal Varices

Without endoscopy, there are no reliable methods of predicting which patients will have varices. It is generally felt that endoscopic screening should be performed in all newly diagnosed cirrhotic patients and all other cirrhotic patients who are medically stable, willing to be treated prophylactically, and would benefit from medical or endoscopic therapies. Those patients with a shortened life expectancy are most likely not going to benefit from prophylactic treatment, so should not be screened. Patients with no varices should have repeat endoscopies at three year intervals, whereas patients with small varices should be screened every one to two years.

Prophylaxis against a First Bleed

Since there is a high mortality rate associated with variceal bleeding, primary prevention is indicated in patients found to have varices. Multiple studies have shown that non-selective beta-blockers like propranolol and nadolol (convenient for its once a day dosing) given in doses that reduce the heart rate by 25% can prevent or delay the first episode of variceal bleeding, and may slow the rate of growth of small esophageal varices. These medications work by lowering portal pressure. Selective beta blockers can reduce portal venous pressure, but the effect is not dramatic, so their use needs to be validated in large scale clinical trials.

Sclerotherapy is not recommended for primary prophylaxis as it may be associated with an increased mortality rate.

Band ligation has been shown to be as effective as beta-blockers; some studies may suggest that it is better. It is generally used as primary prophylaxis in patients at high risk for bleeding, and in those who either cannot tolerate beta-blockers or have contraindications to its use.

Important to ask whoever is with the patient if they have noticed these subtle changes.

Despite the numbers of patients who have this complication of cirrhosis, the pathogenesis of hepatic encephalopathy is poorly understood. It is thought that the accumulation of unmetabolized ammonia, mainly as a result of poor hepatic function and portosystemic shunting, plays an important role. Although other mechanisms have been proposed, the mainstays of treatment are based on the ammonia hypothesis.

Diagnosis

The first step in diagnosis is to exclude other etiologies including metabolic and toxic encephalopathies, intracranial lesions, and other neuropsychiatric disorders. Besides history and physical, there is no specific diagnostic test one can perform to diagnose hepatic encephalopathy. Logically one would think that if it were a problem with accumulation of ammonia, such a level should be helpful in diagnosis. In clinical practice, use of an ammonia level remains controversial. The actual ammonia level is poorly correlated with the grade of hepatic encephalopathy. There are many factors that can influence the accuracy of ammonia testing, including fist clenching and whether the sample was placed on ice. As well, ammonia levels can be elevated as a result of non-hepatic conditions. It may be useful in certain conditions; for instance if the ammonia level is completely normal, it can help the push to look for other causes of encephalopathy. In general it is not required to make the diagnosis, nor is it required in the long-term follow-up of patients with cirrhosis.

Another important consideration in the diagnosis of hepatic encephalopathy is if there is a precipitating event. In fact, most episodes of hepatic encephalopathy in patients with cirrhosis are due to a clinically apparent precipitating event.

Common precipitating factors:
- Hypovolemia
- Gastrointestinal bleeding
- Hypokalemia and/or metabolic alkalosis
- Hypoxia
- Sedatives and tranquilizers
- Hypoglycemia
- Infections (including SBP)
- Rarely hepatoma and/or vascular occlusion (hepatic or portal vein thrombosis)
- Uremia/azotemia
- Constipation
Hepatic Encephalopathy

Hepatic encephalopathy is characterized by potentially reversible neuropsychiatric abnormalities which are seen in patients with liver dysfunction. Before making the diagnosis of hepatic encephalopathy, unrelated neurologic and/or metabolic abnormalities have to be excluded. Clinically hepatic encephalopathy can manifest in a broad spectrum of symptoms from subtle abnormalities that can only be found by psychometric testing (known as subclinical hepatic encephalopathy or minimal hepatic encephalopathy) to deep coma. Including patients with subtle abnormalities, hepatic encephalopathy can be present in 50-70% of all patients with cirrhosis.

Grading System for Hepatic Encephalopathy:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Consciousness</th>
<th>Personality and Intellectual Function</th>
<th>Neurologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>Subclinical</td>
<td>Normal</td>
<td>Abnormalities only on psychometric analysis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Inverted sleep pattern, restlessness</td>
<td>Forgetfulness mild confusion, agitation, irritability</td>
<td>Tremor, apraxia, incoordination, impaired handwriting</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy, slow responses</td>
<td>Disorientation as regards time, amnesia, decreased inhibitions, inappropriate behavior</td>
<td>Asterixis, dysarthria, ataxia, hypoactive reflexes</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence but rousability, confusion</td>
<td>Disorientation as regards place, aggressive behavior</td>
<td>Asterixis, hyperactive reflexes, Babinski signs, muscle rigidity</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>None</td>
<td>Decerebration</td>
</tr>
</tbody>
</table>

In looking at the table, note that the first, recognizable sign of hepatic encephalopathy is the inverted sleep pattern, which should be asked about. Also notice that, in the early stages of encephalopathy, patients can have mild personality changes, which their close contacts may perceive. So, it is

Management of the Acute Variceal Hemorrhage

The three targets of treatment are:

1. Resuscitation,
2. Treatment of bleeding, and
3. Prevention and/or treatment of complications.

Actually, the complications can lead to death more often than the bleeding itself. The main complications which are associated with death are: aspiration pneumonia, sepsis, hepatic encephalopathy, and renal failure.

Resuscitation involves infusion of fluids, blood to keep the hematocrit around 25, and the correction of any coagulopathy that may be contributing to the bleeding. One caveat is to avoid volume overload as this may increase portal pressure and exacerbate the bleeding. Treatment of the bleeding involves medical measures like octreotide and therapeutic measures that are performed during endoscopy.

Along with the above, a thought should be given to elective intubation for airway protection, especially in cases where the patient is obtunded, intoxicated, or has ongoing active hematemesis.

Octreotide

Octreotide works by inhibiting the release of vasodilator hormones like glucagon, which indirectly causes splanchnic vasoconstriction leading to decreased portal inflow. The decrease in portal and intravariceal pressures happen within seconds. It is generally a well tolerated treatment with a low risk of adverse events. Any presentation suspicious for a variceal bleed, should be placed on intravenous octreotide. The dose is 50 μg IV bolus followed by 50-100 μg/hr continuous infusion for 48-72 hr. Studies have shown that octreotide plus endoscopic treatment is better than either modality alone for control of bleeding.

Endoscopic Treatment

The best endoscopic treatment for variceal bleeding is variceal band ligation – a technique developed at UCHSC by Drs. Stiegmann and Goff. “Banding,” as we often call it, works by capturing all or part of a varix with a small elastic band, which results in occlusion from thrombosis. Afterwards, the tissue necroses and sloughs off leaving a superficial mucosal ulceration, which quickly heals. Another endoscopic treatment modality is sclerotherapy. Sclerotherapy involves injection of a sclerosant directly into the varices causing blood clots to form and discontinuation of bleeding. If it is injected
into the area beside the varix, it stops bleeding by thickening and swelling the vein to compress the blood vessel. Numerous studies have confirmed the superiority of banding over sclerotherapy for all major outcomes such as recurrent bleeding, local complications, time to variceal obliteration, and survival.

The American Association for Gastrointestinal Endoscopy (ASGE) recommends the use of band ligators for actively bleeding varices, and recommends that the procedure should be performed every two to four weeks until the varices are eradicated. Sclerotherapy is recommended if banding fails. In the case of gastric varices, although endoscopic treatment may be effective, there is not enough data to recommend a specific type of treatment. In general, endoscopic treatment is not as effective in the case of gastric varices as it is in esophageal varices. Despite treatment, these patients tend to have higher re-bleeding and mortality rates. As far as trying to obliterate gastric varices, there is also not enough data to recommend it as useful, so it is not routinely performed.

Treatment Failure

If the patient continues to bleed despite the above treatments, or re-bleeds, a second attempt at endoscopic hemostasis is usually attempted. If this repeated attempt fails to work and the patient is continuing to bleed, the next step is balloon tamponade. Balloon tamponade is an effective way to achieve short term hemostasis, but, once the balloon is deflated, the patient is at high risk for re-bleeding. For this reason, patients in this situation need to be assessed for transjugular intrahepatic portosystemic shunt (TIPS) as a more definitive treatment for the bleeding. Surgical options can also be considered, but due to adverse events associated with the surgery and the effectiveness of TIPS, surgery is rarely performed. TIPS appears to be as effective for short term control of bleeding gastric varices as esophageal varices. When used in this situation, TIPS is really only a temporary bridge or salvage therapy until definitive treatment with liver transplantation.

Prophylactic Antibiotics

Up to 20% of patients with cirrhosis who come in with bleeding have bacterial infections, and up to 50% more will develop an infection in the hospital. These patients are at risk for sepsis and, obviously, increased risk of death. Common types of infection include urinary tract infections, spontaneous bacterial peritonitis (SBP), respiratory infections, and bacteremia itself. Studies have shown that the use of prophylactic antibiotics in this setting leads to an overall reduction in complications of infection and mortality.

Most studies have used a quinolone, but other regimens included cephalosporins, a quinolone with amoxicillin-clavulanate, non-absorbable antibiotics, and imipenem-cilastin. UpToDate recommends using a quinolone for seven to ten days. At UCHSC, quinolone use is restricted, so an alternative antibiotic has to be used – cephalosporins are a good choice, or per Dr. Levi (ID) ertapenem. The patient can then be switched to a quinolone on discharge.

Prevention of Renal Toxicity

Renal failure in this situation can be seen either as acute tubular necrosis or hepatorenal syndrome. The risk of renal complications can be minimized by appropriate volume replacement and avoidance of nephrotoxins like aminoglycosides.

Hepatic Encephalopathy

If hepatic encephalopathy develops, it is important to remember to look for other factors that can cause it, like SBP. The treatment is the same as that outlined in the hepatic encephalopathy section.

Re-bleeding

There is a period of about six weeks in which these patients are at high risk of recurrent bleeding. The greatest risk is within the first 48 – 72 hours, and over 50% of all early re-bleeding occurs within the first 10 days. Risk factors for re-bleeding during this time include: age > 60, renal failure, large varices, severe initial bleeding, severity of liver disease, ascites, active bleeding seen on esophagogastroduodenoscopy (EGD), red signs on the varices, or a platelet clot on the varix.

The best approach for prevention of another variceal bleed is not clear. Combination therapy with a beta-blocker plus endoscopic band ligation may be more effective than band ligation alone. Because there are no good guidelines as to what to do, treatment is based on physician and patient preferences.

Isolated Gastric Varices

Although isolated gastric varices can be seen in patients with cirrhosis, it is important to remember that it can also be seen in patients with splenic vein thrombosis. In this situation, the treatment of choice would be splenectomy.