

EPEEC-O

Education in Palliative and End-of-life Care - Oncology

Participant's Handbook

Module 3d:

Symptoms -

Ascites

**Emanuel LL, Ferris FD, von Gunten CF, Von Roenn J.
EPEC-O: Education in Palliative and End-of-life Care for Oncology.
© The EPEC Project,TM Chicago, IL, 2005**

ISBN: 0-9714180-9-8

Permission to reproduce EPEC-O curriculum materials is granted for non-commercial educational purposes only, provided that the above attribution statement and copyright are displayed. Commercial groups hosting not-for-profit programs must avoid use of EPEC-O materials with products, images or logos from the commercial entity.

The EPEC ProjectTM was created with the support of the American Medical Association and the Robert Wood Johnson Foundation. The EPEC-O curriculum is produced by The EPEC ProjectTM with major funding provided by the National Cancer Institute, with supplemental funding provided by the Lance Armstrong Foundation. The American Society of Clinical Oncology partners with the EPEC-O Project in dissemination of the EPEC-O Curriculum. Acknowledgment and appreciation are extended to Northwestern University's Feinberg School of Medicine, which houses The EPEC Project.

Special thanks to the EPEC-O Team, the EPEC-O Expert Panel, and all other contributors.

Accreditation Statement

The Northwestern University Feinberg School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Visit www.epec.net to order EPEC materials, access On-line Distance Learning, or for further information.

Contact EPEC by E-mail at info@epec.net, or

The EPEC ProjectTM
750 N. Lake Shore Drive, Suite 601
Chicago, IL 60611
USA

Phone: +1 (312) 503-EPEC (3732)

Fax: +1 (312) 503-4355

Case*

Q.H. is 44-year-old disabled truck driver admitted to a hospice program with hepatoma and ethanol-induced cirrhosis. A diminished albumin level and elevated prothrombin time are consistent with impaired hepatic synthetic function. Comorbidities related to cirrhosis include esophageal varices, a single, recent episode of hepatic encephalopathy, coagulopathy, and massive ascites. Although abstinent from ethanol for the preceding five years, he is not a liver transplantation candidate because of significant cardiopulmonary disease. Medications include furosemide 40 mg PO tid, spironolactone 200 mg PO bid, lactulose 30 mg PO tid, thiamine 100 mg PO daily, folate 1 mg PO daily, pantoprazole 40 mg PO daily, paroxetine 20 mg PO daily, albuterol MDI 2 puffs q 4 h PRN, ramipril 2.5 mg PO daily, and O₂ 2 l/min. The physical examination shows no jugular venous distension. The abdomen is obese, but shifting dullness and a fluid wave are demonstrable. There is no asterixis. Laboratory examination is remarkable for a partial prothrombin that is elevated by \approx 4 seconds above normal. The platelet count is 65,000/ μ l.

* This case is not on an EPEC-O Curriculum trigger tape.

Introduction

Ascites is *the accumulation of fluid in the abdomen*. Its formation may be a direct result of a malignant process or secondary to an unrelated comorbidity. Ascites may be responsible for or contribute to dyspnea, early satiety, fatigue, and abdominal pain.

Because the pathophysiology of fluid collection varies, treatment strategies differ. An understanding and clinical differentiation of the mechanisms responsible for ascites are imperative for rational management.

Prevalence

Ten percent of all ascites is caused by malignancy. Epithelial malignancies, particularly ovarian, endometrial, breast, colon, gastric, and pancreatic carcinomas, cause over 80 % of malignant ascites. The remaining 20% are due to malignancies of unknown origin.¹

Prognosis

In general, the presence of ascites portends a poor prognosis. The mean survival in patients with malignant ascites is generally less than 4 months. However, with ascites due to a malignancy that is relatively sensitive to chemotherapy, eg, newly diagnosed ovarian cancer, the mean survival may be significantly better, ie, 6–12 months.

Pathophysiology

Complex mechanisms are responsible for malignant ascites. Liver metastases can cause hepatic venous obstruction and result in portal hypertension. Increased portal pressure leads to transudation of fluid across the splanchnic bed into the abdominal cavity.

The ascites of peritoneal carcinomatosis accumulates via a different mechanism. Tumor cells on the peritoneal surface directly interfere with normal venous and lymphatic drainage, causing fluid to ‘leak’ into the abdomen. A humoral vascular permeability factor that allows exudation of fluid from the peritoneal vessels has also been identified.² Chylous ascites can result from the lymphatic obstruction commonly seen in lymphoma.

In cancer patients, diminished intravascular oncotic pressure resulting from hypoalbuminemia may exacerbate ascites accumulation. Any of these mechanisms may be complicated by the abnormal sodium and fluid retention of comorbid cirrhosis or congestive heart failure.

Other comorbid causes of nonmalignant ascites are tuberculosis, nephrogenic ascites related to hemodialysis, pancreatic disease, portal vein thrombosis, pericardial disease, and nephrotic syndrome.

Assessment

A history of dyspnea, fatigue, anorexia, early satiety, nausea, vomiting, pain, or diminished exercise tolerance in the setting of weight gain, increases in abdominal girth (with or without protrusion of the umbilicus), a sensation of fullness or bloating, and early satiety suggest the presence of ascites. Some people simply describe a vague generalized abdominal discomfort or a feeling of heaviness with ambulation. Increased intra-abdominal pressure can produce esophageal reflux symptoms. Delayed gastric emptying may prompt complaints of indigestion, nausea, and vomiting.

The diagnosis is supported by physical findings of bulging flanks, flank dullness (if fluid accumulation is > 1,500 ml), shifting dullness, and a fluid wave. To monitor changes in ascites volume, measure abdominal girth at the umbilicus or another landmark. Assess for jugular venous distention. If present, it may indicate a potentially reversible cardiac cause of ascites.

A plain radiograph of the abdomen may demonstrate a hazy or ‘ground-glass’ pattern. Ultrasound or computed tomography will identify as little as 100 ml of free fluid, and will be helpful if loculation is present.

A diagnostic paracentesis of 10 to 20 ml of fluid will confirm the presence of ascites. More importantly, determining the serum-ascites albumin gradient (SAAG) will indicate whether portal hypertension is present or not and will direct therapy.

The SAAG is calculated by subtracting the ascitic fluid albumin concentration from the serum albumin concentration.³ Patients with a SAAG of 1.1 g/dl or more have ascites that is due, at least in part, to increased portal pressures. Patients with a SAAG of less than 1.1 g/dl do not have portal hypertension. These correlations are accurate to 97%. The SAAG is superior to, and has superseded the exudate/transudate characterizations that are based solely on ascitic fluid protein concentrations. In general, a high SAAG predicts diuretic responsiveness. One exception is the nephrotic syndrome where, although the SAAG is low, it is typically responsive to diuretics.

Several other diagnostic tests may be useful. Cytologic analysis is the most specific test to demonstrate malignant ascites. It is about 97% sensitive with peritoneal carcinomatosis, but is poor in detecting other types of malignant ascites. Cell counts with a differential are useful in the presumptive diagnosis of bacterial peritonitis, particularly if the neutrophil count is greater than 250 cells per ml. If infection is suspected, a Gram stain and culture should be performed. Direct inoculation of the ascitic fluid into blood culture bottles increases the sensitivity of detecting infection up to 85%.

Management

Every intervention has associated burdens and benefits that need to be realistically considered and discussed, so assess overall goals for patient care before making specific choices for managing ascites. No treatment is needed for the patient who is asymptomatic. Establish prognosis, expected response to management of the underlying conditions, and preferences for treatment before any plan of care is instituted.

Sodium and fluid balance

When portal hypertension is present (high SAAG), dietary management may be helpful. Symptoms may be improved with sodium restriction.⁴ Limiting sodium intake to 88 mmol or 2 gm per day (equivalent to 5 gm of sodium chloride per day) is an attainable goal for a motivated patient but does make food less palatable. Depending on the patient's prognosis and goals of care, it may be better to liberalize the sodium intake and control ascites through other methods. Patients with ascites are also prone to develop dilutional hyponatremia. In patients with advanced disease whose treatment goals are purely palliative, fluid restriction to 1 liter per day is usually intolerably burdensome. Serum sodium levels gradually dropping to as low as 120 mmol per liter may be well tolerated and rarely dictate restrictive intervention.

Diuretics

Diuretic therapy is useful for some patients, particularly those with a component of portal hypertension (high SAAG). It is the goal of diuretic therapy to achieve a slow and gradual diuresis that does not exceed the capacity for mobilization of ascitic fluid. Mobilize only enough fluid to promote comfort. In patients with ascites and peripheral edema, the edema will act as a fluid reservoir to buffer the effects of a rapid contraction of plasma volume. A net diuresis of approximately one liter per day is safe. Symptomatic orthostatic hypotension from intravascular volume contraction is more likely to occur in patients without edema. In this group, a net diuresis of 500 ml per day is more reasonable. Overly aggressive diuretic therapy in patients with ascites due to cirrhosis has been associated with hepatorenal syndrome and death. There are no published reports of hepatorenal syndrome associated with malignant ascites.

In patients with ascites for whom diuretics may be helpful, the renin-angiotensin-aldosterone system is activated. Therefore, the initial diuretic of choice is a distal tubule aldosterone antagonist.

Table 1: Diuretics

Diuretic	Major site of action	Dosage range
Spironolactone	Distal tubule	100-400 mg/day
Amiloride	Distal tubule	10-40 mg/day
Triamterene	Distal tubule	100-300 mg/day

Amiloride is faster acting and may be used as an alternative if painful gynecomastia develops.

Because these diuretics are relatively potassium sparing, advise patients to avoid potassium salt substitutes.

Diuretics act on different segments of the nephron and may produce a synergistic response. If response to spironolactone is suboptimal, a loop diuretic may be added. This combination may affect a more rapid diuresis while maintaining potassium homeostasis.

- Start with a ratio of 100 mg of spironolactone to 40 mg of furosemide. Adjust the ratio and the doses to maintain normokalemia. The dosages can be increased in parallel until the goals of therapy have been attained (not to exceed maximal doses, ie, spironolactone 400 mg PO daily and furosemide 240 mg PO daily), or until therapy is limited by adverse effects.
- Alternately, substitute Ethacrynic acid, 50-200 mg PO daily instead of furosemide.

The sequential addition of diuretics is usually recommended. Although there is no evidence to support the combined use of multiple types of diuretics at the beginning of therapy, this may be an appropriate management strategy in a population with limited life expectancy and distressing symptoms. Precious time may be gained by starting with a spironolactone/furosemide combination in the ratios described above.

Diuretic therapy may be excessively burdensome in patients with limited mobility, urinary tract outflow symptoms such as hesitancy and frequency, poor appetite and poor oral intake, or complex polypharmacy. Injudicious use of diuretics can result in incontinence with attendant self-esteem and skin care issues, sleep deprivation from frequent urination, fatigue from hyponatremia and/or hypokalemia, and falls caused by postural hypotension.

Nonsteroidal anti-inflammatory medications can alter glomerular filtration and inhibit prostaglandin promotion of sodium and water excretion. Their discontinuation may increase diuretic efficacy.

If these medication interactions have been minimized, salt intake is appropriate, and there is no response to maximal diuretic therapy, the ascites is considered refractory.

Therapeutic paracentesis

Paracentesis may be the only therapeutic modality that is effective, particularly for patients with low SAAG. The symptom response is much faster than when diuretics are used alone.

If the ascites is in equilibrium with the systemic circulation, as is the case with portal hypertension (high SAAG), there is a risk of hemodynamic compromise. This is not true for patients with low SAAG. Colloid plasma volume expansion, eg, 6-8 gm of albumin per liter of ascites removed, has been used to avoid this complication, but its use remains controversial. Albumin is expensive, but it is not known to cause harm. Large-volume therapeutic paracentesis (≥ 5 liters) with concurrent colloid infusion is a simple procedure and is associated with minimal morbidity or mortality. Practitioners may opt to use colloid for large volume paracentesis of ascites due to portal hypertension (high SAAG) until more definitive guidelines exist.

Implanted external catheters

Tenckhoff or other implanted abdominal catheters may be beneficial for selected patients who require repeated large-volume paracentesis for comfort and whose prognosis warrants an invasive procedure.⁵ Under local anesthesia, an externally draining catheter is surgically placed in the peritoneal cavity.

This drain can be conveniently accessed intermittently by physicians or nurses, or even by trained family members. The comfort and advantage of the smaller, less obtrusive devices is offset by their tendency to occlude. To date, there are no studies comparing implanted catheters with serial paracentesis in patients with either cirrhotic or malignant ascites. Complications such as cellulitis, peritonitis, asymptomatic culture positive ascites, and fibrin clots have been reported. With no guidance from the literature, the clinician must individualize the use of implanted catheters.

Peritoneovenous shunts

Surgically placed peritoneovenous shunts have been used for management of malignant and nonmalignant ascites. The 30 to 60 minute procedure is performed under local anesthesia. These shunts drain ascites from the peritoneal space via a one-way valve into the thoracic venous system. Unfortunately, the rate of complications is high, including shunt occlusion, heart failure due to fluid overload, infection, and disseminated intravascular coagulation. In malignant ascites, studies have found no improvement in survival or quality of life. Thus, although there may be specific cases where peritoneovenous shunting is advantageous, serial paracentesis remains the first line therapy.

Transjugular intrahepatic portosystemic shunt

The transjugular intrahepatic portosystemic shunt (TIPS) is a procedure performed by interventional radiologists that creates a side-to-side shunt that effectively relieves portal

hypertension. For patients with cirrhosis and refractory ascites who have relatively good hepatic and renal functions, TIPS is considered the treatment of choice. However, shunt malfunction rates of up to 40% have been reported. In two cases of malignant portal and hepatic vein occlusion, TIPS improved ascites and quality of life.⁶ As with any palliative management option, the decision to pursue invasive surgical procedures is dependent on the patient's goals and the disease context.

Summary

Malignant ascites is associated with a poor prognosis. Determination of the SAAG helps determine whether diuretics with or without dietary modifications are likely to be effective. Paracentesis can relieve symptoms. In selected patients, placement of a permanent catheter may be warranted.

Key take-home points

1. Malignant ascites is due to increased portal pressures, direct secretion into the abdomen, or a combination of these two mechanisms.
2. Calculation of the serum-ascites albumin gradient (SAAG) helps determine whether diuretic therapy is likely to be of benefit; a gradient of >1.1 g/dl is associated with portal hypertension.
3. Intermittent physical removal of fluid, either with intermittent paracentesis or placement of an intraperitoneal catheter, relieves discomfort in selected patients.

Pearls

1. Ask about how well clothes fit to assess girth and rate of change.
2. The time spent at the bedside doing a paracentesis is an opportunity for an extended conversation.
3. A chronic leak after paracentesis is not always bad; it may diminish the need for a repeat procedure.

Pitfalls

1. Don't lose sight of overall goals. For example, a patient who develops postural hypotension and/or fatigue from aggressive diuresis and falls is worse off than someone with only a large belly.
2. A patient who is asymptomatic cannot have his or her symptoms improved.

References

¹ Runyon BA, Hoefs JC, Morgan TR. Ascitic fluid analysis in malignancy-related ascites. *Hepatology*. 1988;8:1104-1109. [PMID: 3417231](#).

A prospective study identified 45 patients with malignancy-related ascites among 448 ascites patients (10% of the total). Patients with peritoneal carcinomatosis but without massive liver metastases (53.3%

of the patients with malignancy-related ascites) had a uniformly positive ascitic fluid cytology, high ascitic fluid protein concentration, and low serum-ascites albumin gradient. Patients with massive liver metastases and no other cause for ascites formation (13.3% of the series) had a negative cytology, low ascitic fluid protein concentration, high serum-ascites albumin gradient, and markedly elevated serum alkaline phosphatase. Those with peritoneal carcinomatosis and massive liver metastases (13.3% of the series) had a nearly uniformly positive ascitic fluid cytology, variable protein concentration, high serum-ascites albumin gradient, and markedly elevated serum alkaline phosphatase. Chylous ascites (6.7%) was characterized by a milky appearance, negative cytology, and an elevated ascitic fluid triglyceride concentration. Patients with hepatocellular carcinoma superimposed on cirrhosis (13.3%) had negative ascitic fluid cytology, low ascitic fluid protein concentration, high serum-ascites albumin gradient, and elevated serum and ascitic fluid alpha-fetoprotein concentration. Two-thirds of patients with malignancy-related ascites had peritoneal carcinomatosis; 96.7% of patients with peritoneal carcinomatosis had positive ascitic fluid cytology.

- ² Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science*. 1983;219:983-985. [PMID: 6823562](#).

Tumor ascites fluids from guinea pigs, hamsters, and mice contain activity that rapidly increases microvascular permeability.

- ³ Hoefs JC. Serum protein concentration and portal pressure determine the ascitic fluid protein concentration in patients with chronic liver disease. *J Lab Clin Med*. 1983;102:260-273. [PMID: 6864073](#).

The ascitic fluid and serum concentrations of albumin and globulin were measured simultaneously with transhepatic portal pressure determination in 56 patients. The majority of variation in ascitic fluid protein concentration between patients with chronic liver disease is associated with differences in portal pressure and serum protein concentrations.

- ⁴ Pockros PJ, Esrason KT, Nguyen C, Duque J, Woods S. Mobilization of malignant ascites with diuretics is dependent on ascitic fluid characteristics. *Gastroenterology*. 1992;103:1302-1306. [PMID: 1397889](#).

Oral diuretics were given to nine patients with ascites caused by peritoneal carcinomatosis, four patients with chylous malignant ascites, and three patients with portal hypertension-related ascites caused by massive hepatic metastases. In patients with ascites caused by peritoneal carcinomatosis or chylous malignant ascites there was no mobilization of ascites, whereas in patients with massive hepatic metastasis, ascites may be mobilized with diuretics.

- ⁵ Barnett TD, Rubins J. Placement of a permanent tunneled peritoneal drainage catheter for palliation of malignant ascites: a simplified percutaneous approach. *J Vasc Interv Radiol*. 2002;13:379-383. [PMID: 11932368](#).

Twenty-nine patients with symptomatic, large-volume malignant ascites underwent percutaneous placement of a tunneled multiple-side-hole Tenckhoff catheter with use of a modified Seldinger technique employing curved and straight coaxial needles. All patients were able to drain their ascites at home and all achieved significant improvement in their symptoms attributable to ascites. Twenty-three of the 29 were outpatients. One patient developed cellulitis, one had persistent leakage around the catheter, one catheter had to be replaced, and one catheter was accidentally removed at home. No patient developed clinical symptoms of peritonitis or sepsis. All deaths were attributable to patients' underlying malignancies.

- ⁶ Burger JA, Ochs A, Wirth K, Berger DP, Mertelsmann R, Engelhardt R, Roessle M, Haag K. The transjugular stent implantation for the treatment of malignant portal and hepatic vein obstruction in cancer patients. *Ann Oncol*. 1997;8:200-202. [PMID: 9093733](#).

In 2 patients, the symptoms of the portal hypertension disappeared after the TIPS procedure. This was accompanied by a significant improvement of the patient's performance status, allowing an early ambulation.