Malignancy-related ascites

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INTRODUCTION

Among patients with ascites in the United States, most (85 percent) have cirrhosis and portal hypertension [1]. Malignancy-related ascites is much less common, accounting for or contributing to ascites formation in approximately 7 percent of patients [1]. Some patients have two causes for ascites formation (eg, cirrhosis plus peritoneal carcinomatosis).

This topic will review malignancy-related ascites. A general approach to the evaluation of patients with ascites, the management of patients with ascites in the setting of cirrhosis, and less common causes of ascites are presented separately. (See "Evaluation of adults with ascites" and "Ascites in adults with cirrhosis: Initial therapy" and "Ascites in adults with cirrhosis: Diuretic-resistant ascites" and "Chylous, bloody, and pancreatic ascites".)

ETIOLOGY AND PATHOGENESIS

Malignancy-related ascites may be seen with several tumors, including malignancies of the ovary, breast, colon, lung, pancreas, and liver. In addition, lymphoma can be complicated by chylous ascites. There is a common misconception that malignancy-related ascites is synonymous with peritoneal carcinomatosis [2]. Malignant disease can cause ascites by at least six mechanisms (table 1) [3]. Thus, the phrase "malignancy-related ascites" is a more appropriate descriptor than "malignant ascites" since it includes all of these causes.

Influence of tumor type — Ascites typically develops in the setting of recurrent and/or advanced cancer. Patients may have a history of metastases to the peritoneum or liver, enlarged abdominal lymph nodes, or a large tumor burden prior to the development of ascites. The origin of the primary tumor has an impact on the sites of abdominal metastases and the etiology of the ascites [3]:

- Malignancies of ovarian and urinary bladder origin as well as peritoneal mesothelioma tend to cause peritoneal carcinomatosis. In such cases, the accumulation of fluid is the result of blockage of the draining lymphatic channels (which normally keep the amount of intraperitoneal fluid low) and increased vascular permeability.

- Colonic, gastric, breast, pancreatic, and lung cancers may cause peritoneal carcinomatosis and/or massive liver metastases, which leads to ascites either because of tumor cells producing fluid into the peritoneal cavity, obstruction/compression of the portal veins leading to portal hypertension, or liver failure.

- Lymphomas may cause lymph node obstruction with the accumulation of chylous ascites [4]. The malignant cells of an effusion from a primary lymphoma involve the serosal surface, leading to symptomatic serous effusions containing high-grade, malignant lymphocytes, but with no detectable mass lesion. (See "Primary effusion lymphoma".)

Patients with underlying liver disease — Malignancy-related ascites in patients with underlying liver disease is usually due to hepatocellular carcinoma (HCC) rather than liver metastases. The development of ascites may be the first indication of a primary HCC.

The four most common settings in which HCC-related ascites develops are in patients with nonalcoholic fatty liver disease, chronic hepatitis C virus, chronic hepatitis B virus acquired in infancy or childhood (most common in Asia), or alcoholic cirrhosis [5]. In these settings, ascites often develops when the tumor volume grows to an extent that it increases portal hypertension by replacing a critical portion of functional liver mass or by invading the portal vein leading to portal vein thrombosis.

HCC that develops in the setting of alcoholic liver disease is often seen in patients with compensated cirrhosis who have stopped drinking and lived long enough to develop HCC. HCC can develop in cirrhosis due to other causes, but in these settings it is frequently detected during surveillance, when the tumor is not large enough to cause ascites. (See "Surveillance for hepatocellular carcinoma in adults", section on 'High-risk groups'.)

CLINICAL MANIFESTATIONS

Patients often first seek medical attention because of abdominal pain, shortness of breath, or early satiety. Abdominal pain may be due to a combination of factors, including nerve invasion by the tumor, stretching of the liver capsule, or (in those with tense ascites) stretching of the abdominal wall. The clinical manifestations of ascites are discussed in detail elsewhere. (See "Evaluation of adults with ascites", section on 'Clinical manifestations'.)

Because ascites usually develops in the setting of a large tumor burden, patients have typically lost a large amount of weight before the development of ascites (despite the added weight from the ascitic fluid itself).

DIAGNOSIS

The diagnosis of malignancy-related ascites is based on the clinical setting, imaging tests, and ascitic fluid analysis [6-8]. (See "Evaluation of adults with ascites", section on 'Diagnosis'.)

Patients with a known malignancy who develop ascites frequently do not require an extensive inpatient evaluation. Because the development of malignancy-related ascites in such patients is a poor prognostic sign, the diagnostic approach should focus on rapid evaluation and discharge, with treatment aimed at improving quality of life (table 2). On the other hand, the presence of ascites in a woman with epithelial ovarian cancer is not necessarily associated with a severely limited prognosis. (See 'Prognosis' below.)

The general approach to the evaluation of patients with ascites is discussed in detail elsewhere. The discussion that follows focuses on the diagnostic findings in patients with malignancy-related ascites. (See "Evaluation of adults with ascites", section on 'Diagnosis'.)

Physical examination — Although rarely present, an umbilical nodule that does not represent herniating bowel or omentum (ie, a Sister Mary Joseph nodule) provides supportive evidence for malignancy as the cause of the ascites. Fine-needle aspiration of the nodule can provide a rapid tissue diagnosis. Gastric cancer, colon cancer, hepatocellular carcinoma (HCC), lymphoma, and rarely peritoneal mesothelioma can cause ascites accompanied by an umbilical nodule.

Imaging tests — Patients with suspected malignancy-related ascites should undergo imaging to confirm the presence of ascites, visualize the liver, and examine for other findings that might support the diagnosis of malignancy. We often start with abdominal ultrasound because it is inexpensive, readily available, and does not require exposure to radiation or contrast. Computed tomography or magnetic resonance imaging may also be performed depending upon the clinical setting and the patient's renal function (eg, in the setting of a suspected extra-hepatic malignancy, such as ovarian cancer).

Abdominal paracentesis — Abdominal paracentesis with appropriate ascitic fluid analysis is the most efficient way to confirm the presence of ascites, diagnose its cause, and determine if the fluid is infected [6-8]. (See "Evaluation of adults with ascites", section on 'Determining the cause of the ascites'.)

Appearance — The gross appearance of the ascitic fluid can be helpful in the differential diagnosis (see "Evaluation of adults with ascites", section on 'Appearance'):

- **Clear fluid** – Uninfected ascites in the setting of cirrhosis or massive liver metastases is usually translucent and yellow; it can be as clear as water if the ascitic fluid bilirubin concentration is normal and the protein concentration is very low (<1 g/dL).

- **Turbid or cloudy** – Ascitic fluid in the setting of peritoneal carcinomatosis may be turbid or cloudy due to the presence of cells. In general, high protein concentrations do not make ascitic fluid turbid or cloudy. An elevated triglyceride concentration of as little as 50 to 100 mg/dL makes the fluid "opalescent."

- **Milky** – Milky fluid usually has a triglyceride concentration greater than serum and greater than 200 mg/dL (2.26 mmol/L; often greater than 1000 mg/dL [11.3 mmol/L]); such specimens are referred to as chylous ascites [9]. A study performed in a tertiary referral center reported that malignancy was the most common cause of chylous ascites [4]; however, the results may have been affected by selection bias [9]. By contrast, a prospective study performed in large general hospitals documented that cirrhosis caused 10 times as many cases of chylous ascites as malignancy [10]. Approximately 1 out of 200 patients (0.5 percent) with cirrhosis has chylous ascites in the absence of cancer [10]. (See "Chylous, bloody, and pancreatic ascites".)

- **Pink or bloody** – Pink fluid usually has a red blood cell concentration of >10,000 cells/mm^3, and frankly bloody fluid typically has a red blood cell count >50,000 cells per mm^3. (See "Chylous, bloody, and pancreatic ascites".)

  Ascitic fluid is bloody in about one-half of patients with HCC and in about 20 percent of patients with malignancy-related ascites overall [3]. Ascitic fluid is bloody in less than 10 percent of patients who have peritoneal carcinomatosis as the sole cause of ascites formation, but it is bloody in about two-thirds of patients with peritoneal carcinomatosis plus massive liver metastases [3].

General ascitic fluid tests — General tests frequently obtained in the evaluation of ascitic fluid include a cell count and differential, serum-ascites albumin gradient (SAAG), cultures,

protein concentration, glucose concentration, and lactate dehydrogenase concentration (table 3) (see "Evaluation of adults with ascites", section on 'Initial ascitic fluid tests'):

- **Cell count and differential** – The total white blood cell count is ≥500 cells/mm^3 in approximately 75 percent of patients with peritoneal carcinomatosis, 80 percent of those with peritoneal carcinomatosis plus massive liver metastases, and 66 percent of those with cirrhosis and HCC [3].

  Peritoneal carcinomatosis can mimic spontaneous bacterial peritonitis; about 8 percent of patients have an absolute neutrophil count ≥250 cells/mm^3 [3].

  The tip-off that the fluid is not infected is the predominance of lymphocytes. The presence of neutrophils may reflect a response to dying tumor cells.

  Antibiotics can be given initially when an elevated fluid neutrophil count is detected. Antibiotics can be discontinued when it becomes clear (by positive cytology and absence of growth on bacterial culture) that ascites is related to malignancy and that infection has been excluded. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Selecting empiric therapy'.)

- **Serum-ascites albumin gradient** – The SAAG accurately identifies the presence of portal hypertension and is more useful than the older protein-based exudate/transudate concept for identifying portal hypertension (table 4) [1]. The SAAG is calculated by subtracting the ascitic fluid albumin value from the serum albumin value, which should be obtained the same day. (See "Evaluation of adults with ascites", section on 'Serum-to-ascites albumin gradient'.)

  - The presence of a gradient ≥1.1 g/dL (11 g/L) is an indicator of portal hypertension with 97 percent accuracy [1]. Patients with HCC-complicating cirrhosis and patients with massive liver metastases (with or without peritoneal carcinomatosis) almost always (94 percent in one study) have a SAAG ≥1.1 g/dL [3].

  - A gradient <1.1 g/dL (<11 g/L) indicates that the patient does not have portal hypertension [1]. Patients with peritoneal carcinomatosis in the absence of cirrhosis or massive liver metastases almost always (95 percent in one study) have a SAAG <1.1 g/dL [3].

- **Cultures** – Bacterial cultures of ascitic fluid should be obtained on specimens from patients with new onset ascites, as well as those with fever or abdominal pain [6,7]. An adequate volume of ascitic fluid (generally 10 mL per bottle, but the amount will vary

according to the manufacturer of the bottle) should be inoculated into blood culture bottles at the bedside. It is unusual to detect spontaneous bacterial peritonitis in patients with ascites due solely to peritoneal carcinomatosis. (See "Spontaneous bacterial peritonitis in adults: Diagnosis".)

Bacterial culture does not need to be repeated when a large volume of fluid is being removed and no fever or unexplained abdominal pain is present.

- **Protein** – The ascitic fluid protein concentration may provide a clue to the cause of the malignancy-related ascites. In one series, the mean ascitic fluid total protein concentration in patients with peritoneal carcinomatosis was 4.0 g/dL, and 95 percent of patients had a value ≥2.5 g/dL when the ascites was due solely to peritoneal carcinomatosis [3]. By contrast, it was always <2.5 g/dL in patients with massive liver metastases and in patients with HCC-complicating cirrhosis. (See "Evaluation of adults with ascites", section on 'Total protein concentration'.)

- **Glucose** – The ascitic fluid glucose concentration is similar to that in serum unless glucose is being consumed in the peritoneal cavity by white blood cells, bacteria, or malignant cells; thus, the concentration of glucose may be low in the setting of peritoneal carcinomatosis. In one series, 70 percent of patients with malignancy-related ascites had an ascitic fluid glucose level of <100 mg/dL and 17 percent had a level <50 mg/dL [3].

- **Lactate dehydrogenase** – Because lactate dehydrogenase (LDH) is a much larger molecule than glucose, it enters ascitic fluid less readily. If the fluid-to-serum LDH ratio is more than 1.0, LDH is being produced in or released into the peritoneal cavity, usually because of the presence of tumor cells or infection. In one series, when ascites was due solely to peritoneal carcinomatosis, the LDH of the fluid was greater than the upper limit of normal for serum in 74 percent of samples, and was greater than the simultaneous serum value in 54 percent of samples [3].

Cytology — Cytology should be sent on all ascitic fluid samples from patients suspected of having malignancy-related ascites. The overall sensitivity of cytology smears for the detection of malignancy-related ascites is 58 to 75 percent [11-13]. The sensitivity of cytology depends upon the number of specimens processed, the quality of processing, and the cause of the malignancy-related ascites. We suggest that at least 50 mL of ascitic fluid be submitted and either hand-carried to the laboratory or placed immediately into a fixative of the laboratory's choice. It is best to coordinate this with the local laboratory prior to obtaining the sample to assure proper processing and thereby maximize sensitivity.

For patients with ascites related to peritoneal carcinomatosis, viable malignant cells are exfoliated into the ascitic fluid [3]. In most cases, cytology will be positive if the fluid is processed optimally and if enough specimens are examined. If handled properly, a sample of 50 mL is often sufficient to make the diagnosis. Handling of the fluid should be coordinated with the local laboratory; some laboratories prefer a hand-carried specimen, while others prefer a specimen that is fixed in alcohol at the bedside. When the processing of the specimen is coordinated with the laboratory, 83 percent of first specimens from patients with malignancy-related ascites are positive or suspicious for malignancy (93 percent if two specimens are sent and 97 percent if three specimens are sent) [3].

However, only about two-thirds of patients with malignancy-related ascites have peritoneal carcinomatosis. The majority of the remaining patients have massive liver metastases, chylous ascites due to lymphoma, HCC, or malignant Budd-Chiari syndrome; these patients almost always have negative cytologies [3].

HCC causes ascites by increasing portal pressure by replacing liver parenchyma with tumor and/or leading to benign or malignant thrombosis of the portal vein [3]. HCC metastasizes to the peritoneum infrequently enough to be the subject of few reports [14-17]. Ordering an ascitic fluid cytology in an attempt to confirm the diagnosis of an HCC is almost always futile.

Peritoneal mesothelioma may be difficult to diagnose cytologically, even in experienced hands [18-20]. It may be especially difficult to differentiate between peritoneal mesothelioma and a serous ovarian carcinoma. In some cases, peritoneoscopy with tissue biopsy may be needed in order to perform immunohistochemistry and electron microscopy [21]. (See 'Laparoscopy' below.)

The clinical utility of newer, more sensitive and specific cytologic techniques including cytometry to detect aneuploidy and magnetic enrichment is not yet established [11,12,22,23].

Unproven or unhelpful tests

- **Carcinoembryonic antigen** – Carcinoembryonic antigen (CEA) is a glycoprotein that is shed from the surface of some malignant cells; detectable levels of this tumor marker can be measured in the serum, and serve as indicators of disease activity. CEA is elevated in a variety of malignancies, predominantly those affecting the gastrointestinal tract.

  Measurement of CEA in ascitic fluid has been proposed as a helpful test for detecting malignancy-related ascites [18,24]. However, both sensitivity [25,26] and specificity [27] are limited, and as a result, the precise value of ascitic fluid CEA levels in the diagnosis and

differential diagnosis of malignancy-related ascites is uncertain. We do not typically measure ascitic fluid CEA levels.

- **Cancer antigen 125** – We do **not** test patients with ascites for cancer antigen 125 (CA 125) either in the serum or in the ascitic fluid. Assays of CA 125 can lead to misleading results when levels are found to be elevated in serum or ascitic fluid. **It is predictably elevated in both serum and ascitic fluid** and uninformed clinicians may inappropriately pursue the diagnosis of ovarian cancer. Inappropriate exploratory laparotomy can cause a fatal down spiral of a patient with cirrhosis. The diagnosis of ascites due to ovarian cancer should be made only on the basis of cytology and not CA 125 levels.

  Virtually all patients, including men, with ascites or pleural fluid of any cause have an elevated serum level of CA 125, presumed to reflect shear forces on mesothelial cells, so elevated serum levels are nonspecific. In one study, the values in patients with chronic liver disease and ascites averaged 321 U/mL [21]. When ascites is controlled, the serum CA 125 level decreases dramatically [21,28]. Similarly, assays of ascitic fluid CA 125 levels are not helpful for differentiating between ascites that is due to ovarian cancer and ascites that is due to tumors or benign causes [29,30].

- **Ascitic fluid "humoral tests of malignancy"** – As noted above, only approximately two-thirds of patients with malignancy-related ascites have peritoneal carcinomatosis, a virtual requirement for having positive cytology. This has led to the misconception that cytology is insensitive for detecting malignancy-related ascites. In truth, cytology is almost 100 percent sensitive in detecting peritoneal carcinomatosis, but one-third of patients with malignancy-related ascites have other mechanisms of ascites formation. In such patients viable tumor cells are not found lining the peritoneum, and the cytology would not be expected to be positive [3,8].

  Multiple ascitic fluid tests (eg, fibronectin, glycosaminoglycans) have been proposed to replace or supplement the cytology [8,31]. However, none of these tests has stood the "test of time," and their use should be discouraged.

Laparoscopy — Laparoscopy with biopsy of peritoneal implants has a sensitivity for detecting peritoneal carcinomatosis that approaches 100 percent [3]. However, optimally processed cytology of the fluid from a simple, minimally invasive paracentesis almost always precludes the need for this invasive procedure, with the possible exception of peritoneal mesothelioma. (See 'Cytology' above.)

Omental biopsy — Successful diagnosis of the cause of ascites has been described using transabdominal ultrasound-guided biopsy of the greater omentum in patients with a

radiologically thickened greater omentum in whom the cause of ascites remained unclear after a more conventional evaluation [32]. A particular sonographic feature of the greater omentum (the "cerebral fissure" sign) was suggestive of tuberculous peritonitis. Such an approach is uncommonly used in the United States. Omental biopsy has also been reported using computed tomography-guidance [33].

TREATMENT

General approach — Therapeutic paracentesis is the primary treatment for peritoneal carcinomatosis from causes other than ovarian cancer (table 2). Peritoneal ports and catheters can be considered for patients who are intolerant of repeated paracenteses, provided clinicians with expertise in their placement are available.

Diuretics may be helpful in patients with portal hypertension (eg, patients with massive liver metastases, cirrhosis with hepatocellular carcinoma, or malignant Budd-Chiari syndrome) and are a reasonable first step in this setting. We do not implement a dietary sodium restriction in patients with malignancy-related ascites so as not to impair their quality of life. Peritoneovenous shunts, such as the Denver shunt, can be placed to minimize the need for paracentesis, if an experienced surgeon or interventional radiologist is available, though results with peritoneovenous shunts are often disappointing. In patients with malignancy-related ascites from advanced ovarian cancer, treatment options include surgical debulking and chemotherapy.

Paracentesis — Therapeutic paracentesis is the mainstay of treatment for peritoneal carcinomatosis that is not due to ovarian cancer. Case series suggest that approximately 90 percent of patients will respond symptomatically to paracentesis, with as little as a few liters of fluid removed [34-36]. Large-volume abdominal paracentesis is usually needed every one to two weeks, although the frequency should be guided by the patient's symptoms (ie, distension, shortness of breath, and early satiety).

Therapeutic paracentesis can be performed in the office, endoscopy unit, or interventional radiology suite. In the United States, therapeutic paracenteses are often performed by interventional radiology nurse practitioners or an interventional radiologist. Hospitalization is not required and intravenous fluid infusion is not needed following paracentesis [37]. The goal in patients with malignancy-related ascites is to efficiently drain all readily removable fluid. This will minimize the time the patient (and the escort who often accompanies the patient) spends undergoing the procedure, while maximizing the amount of time before the next paracentesis is required. In one study, the adoption of guidelines to minimize the need for image guidance,

decrease the length of time needed to accomplish paracentesis, and eliminate albumin infusion post-paracentesis led to a more efficient procedure with no hypotension [37]. As a result, the authors changed their policies, noting that "some practices were placing unnecessary burdens on patients whose life expectancy was short" [37].

For hospice patients with symptomatic recurrent ascites requiring frequent large-volume paracentesis, home-based paracentesis may also be an option, provided a qualified clinician, nurse-practitioner, or clinician's assistant is available to perform the procedure. One case series of home-based paracentesis reported safe and successful drainage of 2 to 4 liters of ascitic fluid in five patients with symptomatic large-volume ascites in the setting of an advanced terminal illness [38]. In that series, a blind puncture was performed in the right lower quadrant using standard sterile technique.

Peritoneal ports or indwelling tunneled catheter drainage systems can be placed to facilitate repeated paracentesis for symptomatic patients with recurrent malignancy-related ascites, although leakage around the insertion site of peritoneal catheters can be a problem [39-48]. These techniques permit removal of the fluid at home by a visiting nurse, the patient, or a family member. Although infection is a potential complication [39-43], the overall risk appears to be low [49] and infections can often be treated without removing the catheter [50]. In a series with 24 patients who underwent 155 drainages using a peritoneal port, 40 (26 percent) were performed at home. Only one patient developed an infection (4 percent of patients, 0.6 percent of paracenteses) [44]. Other grade 3 or 4 complications included hypoalbuminemia (three patients), hypotension (one patient), and hyponatremia (one patient). Contraindications include single or multifocal loculated pockets of ascites, peritonitis, or uncorrected coagulopathy [46,48].

Unlike patients with ascites due to portal hypertension, patients with malignancy-related ascites can have large volumes of fluid (up to 21 liters) removed without fear of hemodynamic sequelae, including circulatory failure [16,51]. The need for colloid replacement to prevent hemodynamic deterioration after large-volume paracentesis remains controversial. Randomized trials of albumin infusion have not been performed specifically in patients undergoing paracentesis for malignancy-related ascites. However, clinical experience suggests that intravenous albumin infusion is generally **not** necessary in patients with malignancy-related ascites. Furthermore, giving albumin increases the time that the patient spends undergoing paracentesis, especially if he or she has to go to an infusion center to receive the albumin. The use of albumin in patients undergoing large-volume paracentesis in the setting of portal hypertension is addressed elsewhere. (See "Ascites in adults with cirrhosis: Diuretic-resistant ascites", section on 'Colloid replacement'.)

In the absence of successful treatment of the tumor itself, peritoneal implants continue to form and as the implants adhere to previously successful paracentesis sites, performing successful paracenteses can become increasingly difficult. Image guidance can help in this setting. Eventually, the fluid becomes more solid and the patient may develop bowel obstruction, which can be fatal. A quality-of-life assessment tool ("Ascites Symptom Mini-Scale") has been developed for evaluating patients with ovarian cancer-related ascites [52].

Diuretics — Diuretics may be effective in some patients with malignancy-related ascites, particularly in those with portal hypertension (eg, from massive liver metastases). There are no randomized trials evaluating the effectiveness of diuretics in malignancy-related ascites, and their use in this setting is inconsistent. In one survey, 61 percent of clinicians prescribed diuretics for patients with malignancy-related ascites, but only 45 percent believed they were effective [34].

Patients with portal hypertension due to massive liver metastases, cirrhosis with hepatocellular carcinoma, or malignant Budd-Chiari syndrome may be more likely to respond to diuretics than patients with peritoneal carcinomatosis [53]. A serum-ascites albumin gradient ≥1.1 g/dL is suggestive of the presence of portal hypertension, and diuretic treatment is a reasonable first step in this setting. Starting diuretic doses are 100 mg/day of spironolactone and 40 mg/day of oral furosemide. These doses should be adjusted upward (while maintaining this ratio) to achieve natriuresis and weight loss. (See "Ascites in adults with cirrhosis: Initial therapy".)

Shunts — A peritoneovenous (PV) shunt, such as the Denver shunt, can be placed to minimize the need for paracentesis, if a surgeon or interventional radiologist who is experienced in the technique is available [54,55]. Among patients with malignancy-related ascites, contraindications to PV shunting include hemorrhagic ascites, a high ascitic fluid protein content (>4.5g/dL), loculated ascites, portal hypertension, bleeding disorders, and cardiac or renal failure. (See "Hepatorenal syndrome", section on 'Peritoneovenous shunt'.)

Although initially there were concerns that malignant cells would be introduced into the systemic circulation by this approach, resulting in bloodborne metastases, this has not been found at autopsy. However, these shunts can be associated with several complications, including pulmonary edema, pulmonary embolism, disseminated intravascular coagulation, infection, and death. In one series of 89 patients undergoing PV shunting for palliation of malignancy-related ascites, the 30- and 60-day mortality rates were 43 and 61 percent, respectively [56]. Among the 38 patients who died within 30 days of surgery, 12 deaths (31 percent) were directly related to a complication of the shunt procedure. In addition, symptomatic relief was achieved in only 57 patients (62 percent) and only 28 patients (31 percent) maintained a patent shunt and lived for >two months. This led the authors to conclude

that PV shunts are of limited utility and that alternative methods are preferred for management of intractable ascites.

Nutritional issues — Patients with malignancy-related ascites often have a poor appetite, and thus a diet or nutritional supplements should be suggested to maximize caloric intake. We generally do not suggest a sodium restricted diet (despite its benefit in ascites due to portal hypertension) since it may adversely affect the patient's quality of life. Patients with malignancy-related ascites have a short life expectancy and typically diuretic doses can be adjusted to compensate for the lack of a sodium restriction. (See 'Prognosis' below.)

Tumor-targeted treatment — Depending in part upon the tumor type, specific tumor-targeted treatments may be appropriate:

- For women with ascites due to newly diagnosed (or suspected) epithelial ovarian, fallopian tube, or peritoneal carcinoma, the treatment of choice will depend on whether the patient is an operative candidate at the time of presentation. Reasonable options include upfront surgical debulking followed by chemotherapy or neoadjuvant chemotherapy [57].

  A large proportion of women with recurrent, platinum-resistant epithelial ovarian cancer develop ascites, which is frequently resistant to systemic chemotherapy. Vascular endothelial growth factor (VEGF) appears to have an important role in permitting tumors to attach to the peritoneum. Although the evidence is limited, systemic administration of VEGF inhibitors (eg, bevacizumab or aflibercept) may provide symptomatic relief in women with refractory ascites. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease", section on 'Recurrent ascites'.)

- Patients with peritoneal mesothelioma, those with diffuse peritoneal adenomucinosis (pseudomyxoma peritonei), and possibly selected patients with isolated peritoneal carcinomatosis from appendiceal or colorectal adenocarcinoma may benefit from aggressive cytoreductive therapy combined with heated intraperitoneal chemotherapy. (See "Well-differentiated neuroendocrine tumors of the appendix" and "Malignant peritoneal mesothelioma: Treatment" and "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer", section on 'CRS with or without HIPEC for peritoneal metastases'.)

- For patients with ascites due to massive liver metastases from breast cancer, diuretics can be administered while tumor-specific therapy is given. Tumor nodules may shrink such that ascites disappears, leaving the imaging diagnosis of "pseudocirrhosis" [58]. This unusual appearance of the liver is due to its distorted appearance after the tumor nodules disappear.

- For other solid tumors with malignancy-related ascites, the prognosis is poor, the role of surgery is not established, and palliative systemic therapy is appropriate provided the patient is able to tolerate it and its use is in keeping with patient's overall goals of care. The specific regimen is chosen based upon the primary site (see appropriate topic reviews). Unfortunately, many patients with sufficient tumor burden to have ascites have already failed standard chemotherapy.

- Intraperitoneal administration of anticancer drugs enables direct contact of extremely high drug concentrations with the malignant lesions within the peritoneal cavity. However, while some studies suggest promise [59-62], a role for intraperitoneal rather than intravenous administration of cytotoxic chemotherapy for patients with malignancy-related ascites and a tumor other than epithelial ovarian cancer is not established.

Other treatments — For some patients, peritoneal drainage and antitumor therapy may not be needed if other palliative care symptom management approaches (eg, for dyspnea, early satiety, or abdominal discomfort) provide adequate symptom control. (See "Overview of managing common non-pain symptoms in palliative care".)

PROGNOSIS

The reported median survival after a diagnosis of malignancy-related ascites ranges from one to four months [34]. Patients with non-ovarian cancer (including effusion lymphoma) have a particularly poor prognosis, with an expected survival of less than three months [63]. On the other hand, the presence of ascites in a woman with epithelial ovarian cancer is not necessarily associated with a severely limited prognosis. (See "Primary effusion lymphoma" and "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Portal hypertension and ascites".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Fluid in the belly (ascites) (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Malignancy-related ascites may be seen with several tumors, including malignancies of the ovary, breast, colon, lung, pancreas, and liver. In addition, lymphoma can be complicated by chylous ascites. There is a common misconception that malignancy-related ascites is synonymous with peritoneal carcinomatosis. Malignant disease can cause ascites by several mechanisms (table 1). Thus, the phrase "malignancy-related ascites" is a more appropriate descriptor than "malignant ascites," since it includes all of these causes. (See 'Etiology and pathogenesis' above.)

- Patients with malignancy-related ascites often first seek medical attention because of abdominal pain, shortness of breath, or early satiety. Abdominal pain may be due to a combination of factors, including nerve invasion by the tumor, stretching of the liver capsule, or (in those with tense ascites) stretching of the abdominal wall. Because ascites usually develops in the setting of a large tumor burden, patients have typically lost a large amount of weight before ascites develops. (See 'Clinical manifestations' above.)

- The diagnosis of malignancy-related ascites is based upon the clinical setting, imaging tests, and ascitic fluid analysis. We suggest the following approach (table 2). It emphasizes rapid evaluation and discharge, with treatment aimed at improving quality of life. (See 'Diagnosis' above.)

- For most patients with non-ovarian causes of peritoneal carcinomatosis who have symptoms from malignancy-related ascites, we suggest repeated large-volume therapeutic paracentesis rather than diuretics (**Grade 2C**). Peritoneal ports and catheters can be considered for patients who are intolerant of repeated paracenteses, provided

clinicians with expertise in their placement are available. However, because survival is short in patients with malignancy-related ascites, patients often do not require a large number of paracenteses. For patients undergoing large-volume paracentesis for malignancy-related ascites, we suggest **not** using colloid replacement with intravenous albumin (**Grade 2C**). (See 'Paracentesis' above.)

In patients with malignancy-related ascites from advanced ovarian cancer, treatment options include surgical debulking and chemotherapy. (See 'Tumor-targeted treatment' above.)

- In patients with portal hypertension due to massive liver metastases, cirrhosis with hepatocellular carcinoma, or malignant Budd-Chiari syndrome, we suggest a trial of diuretics rather than repeated large-volume paracentesis (**Grade 2C**). Such patients can be identified by a serum-ascites albumin gradient (SAAG) ≥1.1 g/dL. Large-volume paracentesis can be used in patients who do not respond adequately to diuretic therapy. (See 'Diuretics' above.)

- In patients with intractable malignancy-related ascites, we suggest **not** using peritoneovenous (PV) shunts (**Grade 2C**). PV shunts have not been shown to reliably provide symptomatic benefit, and periprocedural morbidity and mortality rates are high. Alternative methods, such as repeated large-volume paracentesis, are preferred for management of refractory malignancy-related ascites. (See 'Shunts' above.)

- Several specific antineoplastic treatments may be useful, depending in part upon the tumor type. For women with ovarian cancer, which is the most common cause of peritoneal carcinomatosis, the treatment of choice will depend on whether the patient is a candidate for surgery at the time of presentation. (See 'Tumor-targeted treatment' above.)

- For some patients, peritoneal drainage and antitumor therapy may not be needed if other palliative care symptom management approaches (eg, for dyspnea, early satiety, or abdominal discomfort) provide adequate symptom control. (See "Overview of managing common non-pain symptoms in palliative care".)

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Topic 1240 Version 36.0

GRAPHICS

Causes of malignancy-related ascites

Cause	Frequency among patients with malignancy-related ascites
Peritoneal carcinomatosis	53 percent
Massive liver metastases causing portal hypertension	13 percent
Peritoneal carcinomatosis plus massive liver metastases	13 percent
Hepatocellular carcinoma plus cirrhosis	13 percent
Chylous ascites due to malignancy, usually lymphoma	7 percent
Budd-Chiari syndrome due to malignancy occluding the hepatic veins	Rare

Data from: Runyon, BA, Hoefs, JC, Morgan, TR. Ascitic fluid analysis in malignancy-related ascites. Hepatology 1998; 8:1104.

Graphic 65840 Version 1.0

Evaluation of the patient with suspected malignancy-related ascites

Select the target population:

- Patients with ascites and suspected or established malignancy*

Perform the following studies:

- Diagnostic paracentesis¶ Δ
- Serum albumin
- Abdominal imaging (eg, computed tomography scan, magnetic resonance imaging)

Determine likely etiology for ascites:

Diagnosis	Fluid cell count◇	Fluid total protein	High fluid triglyceride level§	Fluid cytology	Imaging features
SAAG <1.1 g/dL¥					
Peritoneal carcinomatosis	High with predominantly lymphocytes	≥2.5 g/dL	No	Positive‡	Peritoneal and omental implants
Malignancy-related chylous ascites	High with predominantly lymphocytes	≥2.5 g/dL	Yes	Negative	Abdominal lymphadenopathy
SAAG ≥1.1 g/dL¥					
Massive liver metastases with portal hypertension	Low	<2.5 g/dL	No	Negative	>50% liver replacement by tumor
Hepatocellular carcinoma with cirrhosis	Low	<2.5 g/dL	No	Negative	Focal lesion(s) in cirrhotic liver†
Malignancy-related Budd-Chiari syndrome	Low	Variable	No	Negative	Extrinsic tumor compression causing narrowing and/or thrombus of the hepatic vein

Refer to UpToDate content on the evaluation and management of malignancy-related ascites.

SAAG: serum-to-ascites albumin gradient.

* Ascites typically develops in the setting of recurrent and/or advanced cancer. Malignancies of ovarian and urinary bladder origin tend to cause isolated peritoneal carcinomatosis without liver

metastases. The most common tumor types causing peritoneal carcinomatosis with liver metastases are colon, gastric, breast, pancreatic, and lung cancers.

¶ The following tests are routinely performed on ascitic fluid when malignancy-related ascites is suspected: Gram stain, aerobic and anaerobic culture, cell count and differential, albumin, total protein, glucose, triglyceride level, cytology.

Δ For patients with suspected malignancy-related ascites, diagnostic paracentesis is performed if it will contribute to the evaluation and/or management.

◇ A high ascitic fluid white blood cell count is defined as ≥500 cells/mm^3.

§ For patients with chylous ascites, fluid triglyceride level is typically above 200 mg/dL.

¥ The SAAG is calculated by subtracting the ascitic fluid albumin value (in g/dL) from the serum albumin value (in g/dL).

‡ For patients with suspected peritoneal carcinomatosis (eg, based on imaging findings) but with negative initial fluid cytology, repeat paracentesis with fluid cytology is warranted.

† For patients at risk for developing hepatocellular carcinoma (eg, those with cirrhosis), the diagnosis can be made with contrast-enhanced computed tomography or magnetic resonance imaging tailored for liver evaluation. Refer to other UpToDate content on diagnosis of hepatocellular carcinoma.

Graphic 126221 Version 2.0

Ascitic fluid laboratory data

Routine	Optional	Unusual	Unhelpful
Cell count and differential	Culture in blood culture bottles	AFB smear and culture	pH
Albumin	Glucose	Cytology	Lactate
Total protein	Lactate dehydrogenase	Triglyceride	Cholesterol
	Amylase	Bilirubin	Fibronectin
	Gram's stain		Glycosaminoglycans

AFB: acid-fast bacteria.

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Graphic 71060 Version 1.0

Classification of ascites by the serum-to-ascites albumin gradient

High albumin gradient (SAAG ≥1.1 g/dL)
Cirrhosis
Alcoholic hepatitis
Heart failure
Massive hepatic metastases
Heart failure/constrictive pericarditis
Budd-Chiari syndrome
Portal vein thrombosis
Idiopathic portal fibrosis
Low albumin gradient (SAAG <1.1 g/dL)
Peritoneal carcinomatosis
Peritoneal tuberculosis
Pancreatitis
Serositis
Nephrotic syndrome

Graphic 81696 Version 5.0

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