SHORT VIEW SUMMARY—cont'd

examination require radiologic evaluation with a computed tomography scan and/or ultrasonography.
- When clinically suspected, CAPD peritonitis is confirmed by a finding of greater than 100 WBCs/mm^3 (predominantly PMN cells) in mostly cloudy dialysate, together with the isolation of a microorganism (90%–95% of cases).

Therapy
- Pending confirmatory studies, empirical antibiotic therapy for suspected primary peritonitis should be initiated (see Table 74.1) on the basis of the most likely pathogens.
- Five days of antibiotic therapy is sufficient in most instances, and oral antibiotic therapy may be an option in selected cases.
- The treatment of secondary peritonitis requires antibiotic therapy (see Table 74.5), along with appropriate medical support, source control, and removal of a diseased organ, necrotic tissue, purulence, blood, feces, and other intraperitoneal foreign material, when present.
- CAPD peritonitis is treated with intraperitoneal antibiotics (see Table 74.6), usually for 10 to 21 days.
- CAPD peritonitis due to fungi is preferably treated with systemic antifungal agents (see Table 74.6).
- Peritoneal dialysis catheter removal is necessary in 10% to 20% of patients, particularly with fungal and nontuberculous mycobacterial infections (see Table 74.7).
- Intraperitoneal abscesses require drainage (with percutaneous catheter or surgical), antibiotic therapy (see Table 74.5), and possibly source control through either radiologic intervention or a surgical procedure.

Prevention
- Primary peritonitis prophylaxis is recommended in cirrhotic patients with ascites who are having a gastrointestinal hemorrhage.
- Long-term antibiotic prophylaxis (e.g., with norfloxacin, ciprofloxacin, or trimethoprim-sulfamethoxazole) is indicated in patients with one or more episodes of primary peritonitis, and in cirrhotic patients with ascitic fluid protein concentrations less than 1.5 g/dL, creatinine ≥1.2 mg/dL, blood urea nitrogen (BUN) ≥25 mg/dL, serum sodium ≤130 mEq/L, or hepatic failure (Child-Turcotte-Pugh score ≥9 and bilirubin ≥3 mg/dL) (see Table 74.2).

Intraabdominal infections can take several forms and include a variety of entities resulting from disease or trauma to both hollow and solid organs located in either the peritoneal cavity or retroperitoneal space. Although the gastrointestinal tract is most commonly involved, the urinary and gynecologic tracts may also serve as the primary source of infection. Intraperitoneal infection may be diffuse or localized into one or more abscesses. Intraperitoneal abscesses may form in dependent recesses, such as the pelvic space or Morison pouch; in the various perihepatic spaces; within the lesser sac; or along the major routes of communication between intraperitoneal recesses, such as the right paracolic gutter. In addition, infection may be contained within the intraabdominal viscera, as in hepatic, pancreatic, splenic, tubo-ovarian, or renal abscesses. Abscesses also frequently form around diseased viscera (pericholecystic, periappendiceal, pericolic, and tubo-ovarian) and between adjacent loops of bowel (i.e., interloop abscesses). In addition, intraabdominal infections are classified according to whether the infection is community acquired (approximately 80%) or health care associated. Moreover, community-acquired infections may be further subdivided into low- or high-risk infections depending on the probability of the presence of drug-resistant bacteria, severity of infection (mild, moderate, severe), and any significant patient comorbidities. These categories help to assist in the management of the patient, selection of antimicrobial therapy, and prediction of outcomes; health care–associated infections are most commonly acquired as complications of previous elective or emergency intraabdominal operations. These are caused by nosocomial isolates particular to the site of the operation and to the specific hospital and unit, all of which possess an increased probability of the presence of antimicrobial-resistant pathogens and bacterial species and fungi not common to the intraabdominal cavity. Intraabdominal infections also can be categorized as uncomplicated or complicated. Although the distinction is not always clear, *complicated* intraabdominal infections historically have been defined as extending beyond the hollow viscus of origin into the peritoneal space, with associated abscess formation or peritonitis, whereas those referred to as *uncomplicated* generally involve intramural inflammation of the gastrointestinal tract or a single organ but have a substantial likelihood of advancing to complicated disease if not properly treated.[1,2] The infection can also be graded from mild to moderate to more severe forms on the basis of accepted physiologic scoring systems and according to the patient's underlying immune status and comorbid conditions.

ANATOMY AND PHYSIOLOGY

The anatomic relationships within the abdomen are important in determining possible sources and routes of spread of infection. The peritoneal cavity extends from the undersurface of the diaphragm to the floor of the pelvis. In men, the peritoneal cavity is a closed space. In women, the peritoneal cavity is perforated by the free ends of the fallopian tubes. The stomach, jejunum, ileum, cecum, appendix, transverse and sigmoid colons, liver, gallbladder, and spleen lie within the peritoneal cavity, some being suspended by a mesentery.

The peritoneal reflections and mesenteric attachments compartmentalize the intraperitoneal space and route, spreading exudate to sites that are often distant from the source (Fig. 74.1). The transverse mesocolon divides the peritoneal cavity horizontally into an upper and a lower space. The greater omentum, extending from the transverse mesocolon and lower border of the stomach, covers the lower peritoneal cavity and further separates the upper from the lower peritoneal cavity (Fig. 74.2). The small bowel mesentery divides the lower peritoneal space.

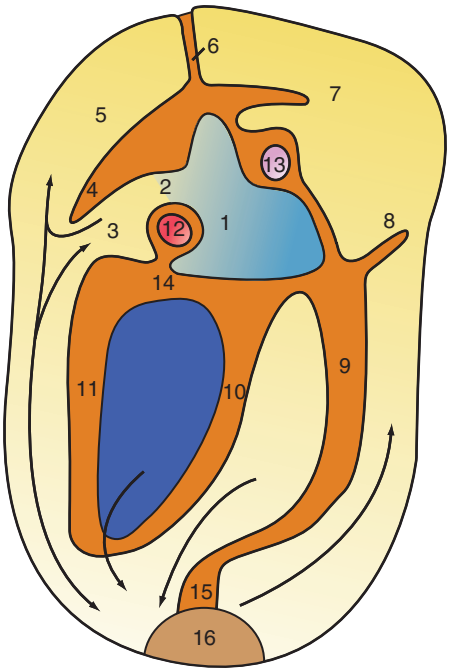

FIG. 74.1 Schema of the posterior peritoneal reflections and recesses of the peritoneal cavity. *1,* Lesser sac; *2,* foramen of Winslow; *3,* Morison pouch; *4,* right triangular ligament; *5,* right subphrenic spaces; *6,* falciform ligament; *7,* left subphrenic space; *8,* phrenocolic ligament; *9,* bare area of the descending colon; *10,* root of the small bowel mesentery; *11,* bare area of the ascending colon; *12,* duodenum; *13,* esophagus; *14,* root of the transverse mesocolon; *15,* bare area of rectum; *16,* bladder.

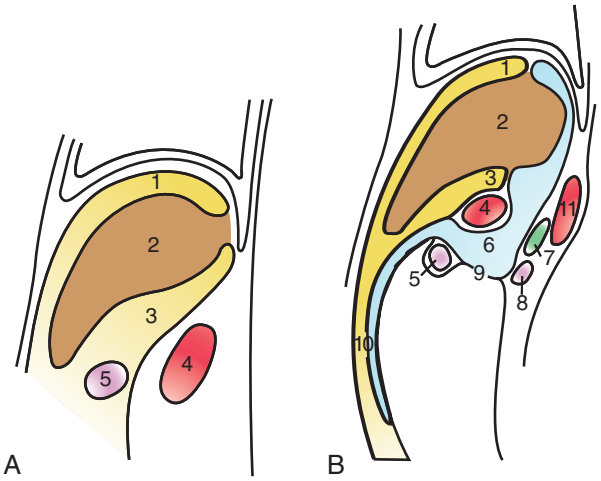

FIG. 74.2 Schema of a sagittal section of the peritoneal cavity. (A) Right upper quadrant. *1,* Subphrenic space; *2,* liver; *3,* subhepatic space; *4,* right kidney; *5,* transverse colon. (B) Left upper quadrant. *1,* Subphrenic space; *2,* liver, left lobe; *3,* subhepatic space; *4,* stomach; *5,* transverse colon; *6,* lesser sac; *7,* pancreas; *8,* duodenum; *9,* transverse mesocolon; *10,* omentum; *11,* left kidney.

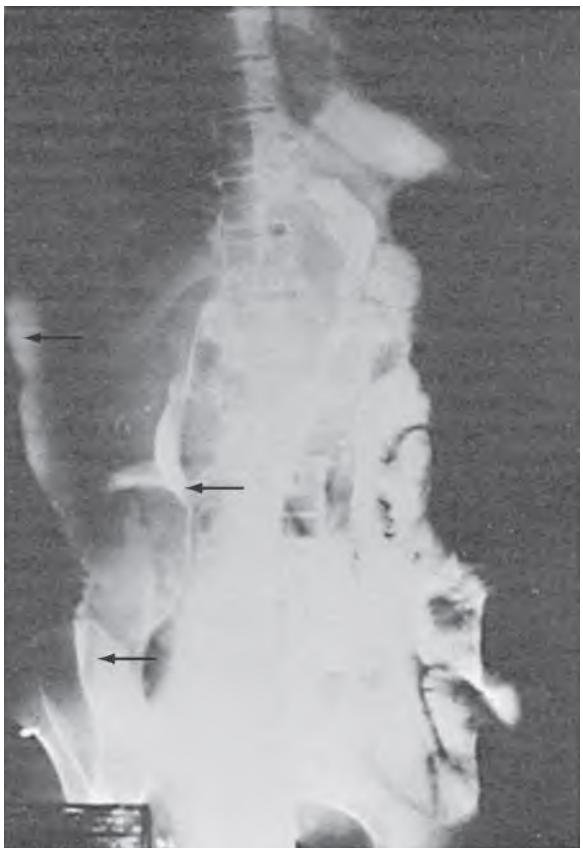

FIG. 74.3 Abdominal radiograph (right decubitus position) after oral administration of radiopaque contrast medium (Gastrografin) to a patient with dehiscence of an esophageal-gastric anastomosis. Radiopaque Gastrografin *(arrows)* can be seen in the subhepatic space, right paracolic gutter, and right subphrenic space and within the lumen of the intestinal tract.

The peritoneal cavity has several recesses into which exudate may become loculated. The most dependent recess of the peritoneal cavity in the supine position is in the pelvis. Between the rectum and bladder in men is a pouch of peritoneal cavity that extends slightly below the level of the seminal vesicles. In women, the uterus and fallopian tubes project into the pelvic recess. Between the rectum and the body of the uterus is the pouch of Douglas, which lies above the posterior fornix of the vagina. On either side of the rectum and bladder are the pararectal and paravesical fossae. The pelvic recess is continuous with the right and the left paracolic gutters.

The phrenicocolic ligament, which fixes the splenic flexure of the colon to the diaphragm, partially bridges the junction between the left paracolic gutter and the left perihepatic space. The right paracolic gutter, in contrast, is continuous with the right subhepatic space and the right subphrenic space. A posterior superior extension of the right subhepatic space, the Morison pouch, is the most dependent portion in the supine position of the right paravertebral groove and lies just above the beginning of the transverse mesocolon. The horizontal posterior reflection of the serosal surface of the liver onto the diaphragm (the right triangular and coronary ligaments) and the vertical reflection (falciform ligament) divide the right perihepatic space into the right subphrenic and right subhepatic spaces (see Figs. 74.1 and 74.2A). The left subphrenic and subhepatic spaces communicate freely around the smaller left lobe of the liver and its more superiorly placed left triangular ligament (see Figs. 74.1 and 74.2B). The right and left subphrenic spaces are separated by the falciform ligament, which probably prevents the spread of pus to the opposite side and explains why only about 5% to 15% of subphrenic abscesses are bilateral. The left subhepatic space is divided by the gastrohepatic omentum into an anterior space and the lesser sac (see Fig. 74.2B). Abscesses within the perihepatic spaces become localized by pyogenic membranes. Abscesses lie anteriorly or posteriorly in the right subphrenic space and superiorly or inferiorly in the subhepatic space. Abscesses of the left perihepatic space are either in the single left subphrenic space or in the lesser sac.

The lesser sac, the largest recess of the peritoneal cavity, is connected to the main peritoneal space by the foramen of Winslow, an opening situated between the free border of the gastrohepatic omentum and the posterior parietal peritoneum. The lesser sac is surrounded posteriorly by the pancreas and kidneys, anteriorly by the stomach, and laterally by the liver and spleen. It may also extend to a variable extent between the folds of the greater omentum. Because of the limited communication from the lesser sac to the major cavity via the foramen of Winslow, suppuration in the lesser sac may exist with little or no involvement of the major cavity. Abscesses in the lesser sac lie between the stomach and the pancreas but may spread to the right and lie anterior to the right kidney and inferior to the liver.

Through intraperitoneal injection of water-soluble contrast material selectively into various intraperitoneal spaces, the right paracolic gutter is demonstrated to be the main communication between the upper and the lower peritoneal cavities. Fluid introduced into the right upper peritoneal space gravitates toward the Morison pouch and then into the right subphrenic space and along the right paracolic gutter into the pelvic recess (Fig. 74.3). Flow of fluid in the left upper peritoneal space is mainly into the left subphrenic space. The phrenicocolic ligament limits flow inferiorly into the left paracolic gutter. Fluid introduced into the lower peritoneal cavity first gravitates to the pelvic recess and then ascends, whether in the supine or erect position, along the right paracolic gutter into the right subhepatic space, especially into the Morison pouch, and into the right subphrenic space. Ascension of fluid from the pelvic space along the left paracolic gutter is minimal and is limited by the phrenicocolic ligament. Although gravity would account for the pooling of fluid in the dependent peritoneal recesses, such as the pelvic recess and Morison pouch, ascension of fluid from the pelvis to the subphrenic space is probably caused by hydrostatic pressure differences between the upper and the lower peritoneal cavities created by diaphragmatic motion. Normal intestinal and abdominal wall motion also accounts for some spread of intraperitoneal fluid.

The retroperitoneal space lies between the posterior peritoneal membrane and the transversalis fascia, extending from the diaphragm to the pelvic brim. In the anterior retroperitoneal space between the peritoneum and anterior renal fascia lie the ascending and descending colons, duodenum, and pancreas. The kidneys and ureters lie within the posterior retroperitoneal (perinephric) space, between the anterior and posterior renal fasciae. The renal fascia encloses the kidneys and

adrenal glands superiorly and laterally, but not inferiorly; this arrangement is favorable for spread of infection in this space inferiorly.

The parietal peritoneum, mainly the anterior portion, is well supplied by somatic afferent nerves and is sensitive to all forms of stimuli. The ability of the anterior parietal peritoneum to sense sharp, well-localized pain in response to local inflammation is crucial for diagnosing abdominal infection and may be associated with involuntary abdominal muscle contraction, tenderness, and rebound tenderness. Irritation of the peripheral diaphragmatic peritoneum is felt as pain near the adjacent body wall, and irritation of the central portion is felt as pain referred to the shoulder. Stimulation of the visceral peritoneum, usually by distention of an organ, causes poorly localized, dull pain.

The peritoneal cavity is lined by a serous membrane. The surface area of this membrane approximates that of the skin. The membrane consists of a monolayer of flat mesothelial cells, beneath which are lymphatic vessels, blood vessels, and nerve endings. Normally, the peritoneal space contains only enough fluid (approximately 100 mL) to maintain moistness of the surface, facilitating movements of the viscera. Noninflamed serous fluid is clear yellow with a low specific gravity (<1.016) and low protein content (usually <3 g/dL). The protein is predominantly albumin. Fibrinogen is not present, and serous fluid does not clot. Solute concentrations are almost identical to concentrations in plasma. A few leukocytes (<250/mm^3), mostly mononuclear cells, and desquamated serosal cells may be present.

The peritoneal membrane is highly permeable. Bidirectional transfer of substances across this membrane is rapid and, because of the large surface area involved, potentially great in quantity. The peritoneal surface, with an approximate area of 1 square meter, has been used extensively as a dialyzing membrane for the treatment of uremia and has been used as a site for the administration of fluid, electrolytes, antibiotics, and blood. The effective serum oncotic pressure and the hydrostatic pressure in the portal veins and lymphatic vessels are major determinants of the rate and direction of fluid movement. The rate of movement of water and solutes between blood and peritoneal fluid also depends on concentration gradients between these compartments and has been studied in detail.[3] Water and solutes diffuse via blood capillaries and, to a lesser extent, through the lymphatic vessels. Lymphatic vessels are involved primarily in removal of nonirritating colloids and particles into the bloodstream. Absorption of particulate matter into lymphatic vessels is thought to occur mostly from the diaphragmatic surface and is aided by the pumping action of diaphragmatic motion. After infusion of radioactive sodium chromate–labeled red blood cells into the peritoneal cavity of dogs, Rochlin and associates[4] found absorption of about 70% of the labeled cells by 48 to 96 hours. This absorption occurred mostly through the lymphatic vessels. In humans, two-thirds of intraperitoneally injected red blood cells in anticoagulated blood have been found in the circulation 8 to 12 days after infusion.[5] The quantity of resorbed cells was lower when no anticoagulant was used with the transfused cells, presumably because of trapping of red blood cells in intraperitoneal clots.[5] Transport of other particulate matter, such as intraperitoneal bacteria, may be similarly impeded because of trapping in fibrinous intraperitoneal exudate.

In addition, communications exist between the peritoneal and pleural cavities that are independent of the bloodstream. In patients with Meigs syndrome, fluid and cells originating in the peritoneal cavity appear in the pleural space, probably as a result of transdiaphragmatic lymphatic transport.

PERITONITIS

Inflammation of the peritoneum may be the result of contamination of the peritoneal cavity with microorganisms, irritating chemicals, or both. Infective peritonitis has been categorized as primary, secondary, or tertiary.[6] Peritonitis complicating peritoneal dialysis can be considered an additional category. In the primary variety, the peritoneal infection is not related directly to other intraabdominal abnormalities. In the secondary variety, peritoneal cavity infections may result from a variety of intraabdominal events, such as a perforation of a hollow viscus (e.g., ruptured appendix, diverticulitis, or a perforated peptic ulcer), ischemic necrosis, or other adverse processes involving the gastrointestinal, gynecologic, or urinary tracts. Tertiary peritonitis has been conceived as a later stage of the disease, when clinical peritonitis and signs of sepsis and multiorgan failure persist or recur after treatment for primary or secondary peritonitis, and no pathogens or only low-grade pathogens (e.g., coagulase-negative staphylococci) or nosocomial, frequently multidrug-resistant, pathogens (e.g., enterococci, *Candida* and *Enterobacter* spp., methicillin-resistant *Staphylococcus aureus*) are isolated from the peritoneal exudate.[7–9] It has been defined as intraabdominal infection that persists or recurs ≥48 hours after successful and adequate surgical source control of secondary peritonitis.[6] Although the transition from one category to another may not always be clear, tertiary peritonitis has a worse prognosis with an estimated mortality rate of 30% to 64%.[10]

Primary Peritonitis

Etiology

Primary peritonitis, sometimes referred to as *spontaneous bacterial peritonitis,* is probably not a specific entity with a common cause but instead represents a group of diseases with different causes that have in common only infection of the peritoneal cavity without an evident source. Primary peritonitis occurs at all ages. The prevalence of primary peritonitis in children apparently has been decreasing.[11] Before the advent of antibiotics, primary peritonitis occurred in about 10% of all pediatric abdominal emergencies; it now accounts for less than 1% to 2%.[12] The decline has been attributed to widespread use of antibiotics for minor upper respiratory tract illness. Although primary peritonitis may occur in children without predisposing disease,[11] it is known to occur particularly in children with postnecrotic cirrhosis[11,13] and in 2% of children with the nephrotic syndrome.[14] In one study, it was also frequently associated with urinary tract infections.[12] In some children with nephrotic disease, repeated episodes of peritonitis occur and peritonitis may precede other manifestations of nephrosis.[11]

Among adults, primary peritonitis has usually been reported in patients with cirrhosis and ascites. The prevalence of primary peritonitis in hospitalized patients with cirrhosis and ascites has been estimated at 10% to 30%.[15] Primary peritonitis occurs in patients with alcoholic cirrhosis,[16–20] postnecrotic cirrhosis,[13] chronic active hepatitis,[16] acute viral hepatitis,[21] congestive heart failure,[22] metastatic malignant disease,[23] systemic lupus erythematosus,[24] or lymphedema and, rarely, in patients with no underlying disease. The presence of ascites resulting from portal hypertension, hypoalbuminemia, peritoneal disease, or other causes (e.g., chylous, myxedema, hemoperitoneum) seems to be the common link among these various conditions. The risk of developing primary peritonitis is greater in patients with high-volume ascites due to advanced cirrhosis (Child-Turcotte-Pugh class C disease, or high Model for End-Stage Liver Disease [MELD] scores) but also increases with a coexisting gastrointestinal hemorrhage, a previous episode of primary peritonitis, a low protein concentration in ascitic fluid (<1 g/dL), elevated serum bilirubin (>2.5 mg/dL), and use of proton pump inhibitors.[15,25–27]

Bacteriologic Characteristics

Primary peritonitis is a monomicrobial infection. Before the 1970s, the organisms reported to cause primary peritonitis in children were *Streptococcus pneumoniae* and group A streptococci.[11,12] By the 1970s, the number of nephrotic children with streptococcal peritonitis had declined and the relative frequency of peritonitis caused by gram-negative enteric bacilli[12,14] and staphylococci[11] had apparently increased.

In cirrhotic patients, microorganisms presumably of enteric origin account for 69% of the pathogens.[28] *Escherichia coli* is the most frequently recovered pathogen, followed by *Klebsiella pneumoniae, S. pneumoniae,* and other streptococcal species including enterococci, and other Enterobacteriaceae.[16,28,29] *Pseudomonas* species are rarely involved.

S. aureus is an unusual isolate in primary peritonitis, accounting for 2% to 4% of cases in most studies, and it has been noted to occur in patients with an erosion of an umbilical hernia. Anaerobes and microaerophilic organisms are reported infrequently. Possible explanations include the intrinsic bacteriostatic activity of ascites against *Bacteroides* spp., the relatively high partial pressure of oxygen in ascitic fluid, and the lack of optimal anaerobic bacteriologic techniques to study patients with primary peritonitis in the past.[30] In a review of 126 cases of primary peritonitis in cirrhotic patients recorded in the literature,

only 8 patients (6%) had disease caused by anaerobic or microaerophilic bacteria, including *Bacteroides* spp., *Bacteroides fragilis, Clostridium perfringens, Peptostreptococcus* spp., *Peptococcus* spp., and *Campylobacter fetus.*[31] Polymicrobial infection was present in four of these eight cirrhotic patients with peritonitis caused by anaerobes, in contrast to the relatively low frequency of polymicrobial infection (only 10 of 118 cases of peritonitis) when aerobes alone were involved.

Three variants of primary or spontaneous peritonitis have been described.[32] One of them, termed *monomicrobial nonneutrocytic bacterascites,* is characterized by ascitic fluid with positive cultures but containing few neutrophils; this condition manifests in patients without clinical findings of peritonitis.[33] It may represent early bacterial colonization before a host response ensues and resolves spontaneously in 62% to 86% of cases, with the remainder progressing to spontaneous bacterial peritonitis, at times within hours. The causative bacteria are similar to those seen in classic primary peritonitis, and patients with a low leukocyte response have the same mortality rate as patients with a greater response.[20] Conversely, several series have identified cases of primary peritonitis with negative ascitic fluid cultures, referred to as *culture-negative neutrocytic ascites.*[34] In one series, sterile cultures occurred in 35% of patients with clinical findings consistent with primary peritonitis, ascitic fluid neutrophil counts greater than 500 cells/mm^3, and no evident source of intraabdominal infection.[34] This variant of peritonitis has been redefined by an elevated ascitic fluid neutrophil count of greater than 250 cells/mm^3, a negative ascitic fluid culture (in the absence of antibiotic therapy or pancreatitis), and no evident intraabdominal, surgically treatable source of infection. Other disorders capable of producing a somewhat similar picture include tuberculous peritonitis, malignancy-related ascites, and any process that leads to death of cells and thereby activates complement or cytokines that can attract leukocytes into the peritoneal cavity. However, in the absence of bacterial infection, the predominance of neutrophils—almost always seen with spontaneous bacterial peritonitis—is not present. Blood cultures have been found to be positive for bacteria in one-third of patients with culture-negative neutrocytic ascites.[34] The frequency of culture-negative ascitic fluid may be decreased by inoculating blood culture bottles with 10 or 20 mL of ascitic fluid at the bedside (see "Laboratory Findings" section).[35]

Last, the third variant of spontaneous bacterial peritonitis, *polymicrobial bacterascites,*[36] is caused by a traumatic paracentesis in which the bowel is entered by the paracentesis needle and bacteria leak, usually transiently, from the gut into the ascitic fluid. This variant occurs in less than 1% of paracentesis procedures, with risk factors that include ileus, the presence of multiple abdominal surgical scars, and intestinal adhesions. In this scenario, various bacterial forms are seen on the Gram stain or grow on culture of the ascitic fluid, which contains fewer than 250 cells/mm^3. If the peritoneal fluid protein concentration is greater than 1 g/dL and the opsonic activity of the fluid is adequate, polymicrobial bacterascites is reported to resolve spontaneously.

Bacteremia is present in 75% of patients with primary peritonitis caused by aerobic bacteria,[28] but it is rarely found in patients with peritonitis caused by anaerobes.[31] Usually the same organisms isolated from the peritoneal fluid are recovered from the blood.[16,31] On occasion, peritonitis results from infection with *Mycobacterium tuberculosis, Neisseria gonorrhoeae, Chlamydia trachomatis,* or *Coccidioides immitis,* but this is usually the result of disseminated infection or sometimes spread from adjacent foci of infection such as the genital tract (see "Pathogenesis" next).

Pathogenesis

The route of infection in primary peritonitis is usually not apparent; it is often presumed to be hematogenous, lymphogenous, or transmural migration through an intact gut wall from the intestinal lumen or, in women, from the vagina via the fallopian tubes. Enteric bacteria have been postulated to migrate from the bowel lumen into mesenteric lymph and to enter the systemic circulation via the thoracic duct; this process is termed *bacterial translocation.*[37] The role of intestinal microbiota bacterial overgrowth is uncertain because different studies have provided conflicting results.[38,39] Enteric bacteria could also enter the systemic circulation from the portal vein by passage through the liver or by portosystemic shunts in patients with portal hypertension.[16] The hepatic reticuloendothelial system is known to be a major site for removal of bacteria from blood. Conn and Fessel[16] postulated that organisms removed from the systemic circulation by the liver contaminate hepatic lymph and pass through the permeable lymphatic walls into the ascitic fluid. Results of animal studies, however, have suggested that destruction of bloodborne bacteria by the reticuloendothelial system is impaired in experimental cirrhosis[40] and in alcoholic liver disease. Infection of ascitic fluid would be facilitated by impaired reticuloendothelial clearance of bacteria from the bloodstream, which would tend to perpetuate bacteremia and increase the opportunity to cause metastatic infection at susceptible sites, such as the ascitic collection. Primary bacteremia, usually caused by coliforms, is a common complication in cirrhosis, and metastatic infection in the pleural space has been reported in cirrhotic patients.[41] An increased frequency of gram-negative endocarditis has also been noted in cirrhotic patients.[42]

In addition, alcohol abuse and cirrhosis have been reported to be associated with impaired intracellular killing by monocytes and neutrophils and with impaired opsonization and low levels of serum complement. The decrease in phagocytic activity seen in alcoholic cirrhosis is proportional to the severity of the liver disease.[43] Impaired local defenses in the peritoneal cavity also facilitate infection of ascites. Opsonic activity, as reflected by low levels of complement and immunoglobulins, is reduced in the ascitic fluid of patients with the nephrotic syndrome and cirrhosis.[44]

Enteric bacteria may also gain access to the peritoneal cavity by directly traversing the intact intestinal wall. In an animal model, *E. coli* passes from the bowel into the peritoneal cavity after the introduction of hypertonic solutions into the peritoneum.[45] A similar mechanism may explain the enteric bacterial peritonitis that frequently complicates peritoneal dialysis. The infrequent occurrence of bacteremia and the multiplicity of species in peritoneal fluid when anaerobic bacteria are involved suggest that transmural migration of bacteria is the probable route of infection of ascitic fluid in most of these patients.[31] In addition, the occurrence of polymicrobial anaerobic peritonitis in two patients after infusion of vasopressin into the superior mesenteric or gastroduodenal arteries suggested that arterial vasoconstriction decreased the intestinal mucosal barrier and permitted transmural migration of enteric organisms.[46] Colonic microorganisms are also known to colonize the upper small bowel in cirrhotic patients.

When pneumococci are present simultaneously in vaginal secretions and peritoneal fluid in prepubertal girls, an ascending infection of genital origin is likely in these patients. The alkaline vaginal secretions of prepubertal girls may be less inhibitory to bacterial growth than the acidic secretions of postpubertal women. Transfallopian spread is also suggested by the development of peritonitis in women with intrauterine devices.[47] In women with gonococcal or chlamydial perihepatitis (Fitz-Hugh–Curtis syndrome), the route of spread is presumably from the fallopian tubes and paracolic gutters to the subphrenic space, but it may also be hematogenous. In the one man documented with this syndrome, *N. gonorrhoeae* was recovered from a liver biopsy specimen and the infection presumably spread by means of bacteremia.[48]

Although tuberculous peritonitis may result from direct entry into the peritoneal cavity of tubercle bacilli (from the lymph nodes, intestine, or genital tract in patients with active disease of these organs), it is more likely to result from hematogenous dissemination from remote foci of tuberculosis, most commonly in the lung. Tuberculous peritonitis can become clinically evident after the initial focus has healed completely.

Bacteria originating from other foci of infections distant from the abdominal or pelvic cavities including the skin and soft tissues, upper and lower respiratory tracts, and odontogenic disease may also hematogenously gain entry into the ascitic fluid.[49]

Infection of ascites stimulates a dramatic increase in proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, interferon-γ (IFN-γ), and soluble adhesion molecules in the serum, and to a much greater extent in the peritoneal exudate.[50] These cytokines are produced by macrophages and other host cells in response to bacteria or bacterial products, such as endotoxin. In an experimental model of peritonitis,[51] antibodies to endotoxin, but not to TNF-α, were found to prevent death and reduce bacterial numbers in the peritoneal exudate. Another potential source is direct translocation of cytokines through

the intestinal barrier. Undoubtedly, many of the systemic and abdominal manifestations of peritonitis are mediated by these molecules. Furthermore, the presence of these cytokines may lead to further reduction of effective arterial blood volume, as indicated by an increase in plasma renin activity and the development of renal insufficiency. Approximately 30% of patients with primary peritonitis develop renal insufficiency, which has been found to be the most sensitive predictor of in-hospital mortality.

Clinical Manifestations

Primary peritonitis is an acute febrile illness often confused with acute appendicitis in children. Fever, abdominal pain, nausea, vomiting, and diarrhea are usually present with diffuse abdominal tenderness and rebound tenderness, and bowel sounds are hypoactive or absent. In cirrhotic patients with primary peritonitis, preexisting ascites is present. In some patients, the clinical manifestations are atypical. The onset may be insidious, and findings of peritoneal irritation may be absent in an abdomen distended with ascites. Fever (temperature >37.8°C [>100°F]) is the most common presenting sign, occurring in 50% to 80% of cases,[16,20] and may be present without abdominal signs or symptoms, or the process may be clinically silent. Primary peritonitis in cirrhotic patients is generally associated with other features of end-stage liver disease (hepatorenal syndrome, progressive encephalopathy, and variceal bleeding). Primary peritonitis should always be considered in the differential diagnosis of decompensation of previously stable chronic liver disease. In approximately 50% of patients with primary peritonitis, mentation is altered, often subtly, because of infection and/or hepatic decompensation. Poor prognostic signs include hypothermia, hypotension, and paralytic ileus.

Gonococcal perihepatitis (Fitz-Hugh–Curtis syndrome) most often occurs in women. It manifests with sudden onset of pain in the right upper quadrant of the abdomen, at times referred to the right shoulder. Low-grade fever, right upper quadrant tenderness, guarding, and a friction rub over the liver may be present. Gonococcal cervicitis or salpingitis may or may not be clinically evident. Chlamydial perihepatitis and gonococcal perihepatitis are clinically indistinguishable.

Primary tuberculous peritonitis is usually gradual in onset, with fever, weight loss, malaise, night sweats, and abdominal distention. The abdomen may not be rigid and is often characterized as being "doughy" on palpation. The findings at operation or laparoscopy consist of multiple nodules scattered over the peritoneal surface and omentum. Adhesions and a variable amount of peritoneal fluid are usually present. Similarly, *C. immitis* can cause a granulomatous peritonitis with a variable clinical manifestation.

Laboratory Findings

Fluid obtained by paracentesis should be examined for cell count, differential count, and total protein and albumin concentrations, and a Gram stain and culture of the fluid should be obtained.[52] It is important that fluid for analysis be obtained before the administration of antibiotics. A polymorphonuclear (PMN) leukocyte count in peritoneal fluid greater than 250 cells/mm^3 is considered diagnostic of primary peritonitis, even when culture of ascitic fluid yields negative results.[15] One potential source of error in the PMN leukocyte count is related to hemorrhage into the ascitic fluid resulting from a traumatic paracentesis, leading to red and white blood cell entry into the fluid. A corrected PMN leukocyte count should be calculated if fluid is bloody, with one PMN leukocyte subtracted from the count for every 250 red blood cells/mm^3 present. The leukocyte count in ascitic fluid may increase, however, during diuresis in patients with chronic liver disease. Studies in which testing for leukocyte esterase has been conducted with use of dipsticks designed for urine have yielded both high and low sensitivities,[53] but this method cannot be recommended at this time.

Nonetheless, the consistently high negative predictive value found with leukocyte esterase reagent strips may support their use as a preliminary screening tool for diagnosis of primary peritonitis.[54] Gram staining of the sediment, when positive, is diagnostic, but it is negative in 60% to 80% of patients with primary peritonitis.[16,19] If multiple bacterial forms are encountered, perforation of the gut needs to be considered. Culture of ascitic fluid may yield negative findings in 40% of patients with clinical manifestations of primary peritonitis and an elevated ascitic fluid PMN leukocyte count.[15,18] In order to optimize the chances of isolating a bacterial pathogen from the fluid, appropriately prepared blood culture bottles should be inoculated with at least 10 mL of ascitic fluid. Culturing ascitic fluid in this manner, as if it were blood, has been shown to increase the culture positivity of patients with an ascitic fluid PMN leukocyte count of greater than 250 cells/mm^3. A positive culture rate increase from about 50% to 77% (with delayed inoculation) to 80% to 100% with immediate inoculation has been demonstrated in individuals who did not receive prior antibiotic treatment and did not have pancreatitis, tuberculous peritonitis, or malignancy-related ascites.[55] Measurement of the ascitic fluid total protein concentration helps distinguish primary peritonitis from secondary bacterial peritonitis. In the latter, the concentration is generally greater than 1 g/dL. Total protein concentration is inversely related to the risk for developing spontaneous peritonitis. Dilute ascitic fluid with a protein concentration less than 1 g/dL poses the highest risk for the development of spontaneous peritonitis because concentrations of opsonins in the fluid are low. The ascitic fluid protein concentration may be low,[16] perhaps because of (1) hypoalbuminemia or (2) dilution of ascitic fluid with transudate from the portal system when cirrhosis is present or the portal vein is obstructed. Calculation of the serum-ascites albumin gradient (SAAG) is useful for indirectly measuring portal pressure. When serum and ascites concentrations are measured simultaneously, a difference of greater than 1.1 g/dL is correlated with portal hypertension with almost 100% accuracy.[56] This difference may be seen with cirrhosis, alcoholic hepatitis, congestive heart failure, the Budd-Chiari syndrome, advanced hepatic metastases, and constrictive pericarditis. Ascitic fluid in tuberculous peritonitis may have an elevated protein concentration (>3 g/dL) and a lymphocytic pleocytosis, but neither may be present, especially in cirrhotic patients.

Various other parameters of ascitic fluid generally considered as optional tests have been suggested to help in diagnosing primary bacterial peritonitis and assist in separating this entity from secondary peritonitis. These include ascitic fluid glucose concentration, which is generally correlated inversely with the number of PMN leukocytes in the fluid. With spontaneous bacterial peritonitis, the glucose concentration usually remains above 50 mg/dL compared with levels that approach zero when peritonitis is secondary to events such as intestinal perforation.[57] Lactate dehydrogenase (LDH) levels (derived from the lysis of PMN leukocytes in ascitic fluid), although increased in spontaneous bacterial peritonitis, are lower than the upper limit of normal for serum. The finding of an elevated amylase concentration in the ascitic fluid is suggestive of gut perforation or pancreatitis. Ascitic fluid found to be dark (orange to brown) in color suggests gallbladder perforation, in which case the ascitic fluid bilirubin concentration that otherwise is low should be measured. Lactoferrin is an iron-binding protein thought to help protect against enteric pathogens by contributing to the antimicrobial effect of neutrophils; although further validation studies may be necessary, levels of lactoferrin have been found to be correlated with the presence of spontaneous bacterial peritonitis.[58] Previously published literature claimed to show the utility of ascitic fluid pH and lactate concentration in helping diagnose primary bacterial peritonitis. However, subsequent larger-scale studies[59] using more accurate methods failed to confirm the usefulness of these tests.

Diagnosis

Primary peritonitis is diagnosed by ruling out a primary intraabdominal source of infection that might result in secondary peritonitis. Distinguishing primary from secondary peritonitis is clinically important, because the latter almost always necessitates either surgical or interventional radiologic source control as a critical component of treatment. In addition, secondary peritonitis usually requires the use of broader spectrum or combination antimicrobial therapy. The signs and symptoms of both forms of peritonitis are frequently not separable. Ascitic fluid analysis and radiologic imaging studies are relied on to distinguish primary from secondary infection. In secondary cases, the ascitic fluid typically contains a total protein >1 g/dL, glucose <50 mg/dL, and LDH level elevated above the upper limit of normal for serum.[57] Polymicrobial infection or the demonstration of multiple morphologic bacterial forms

is suggestive of gastrointestinal perforation. Ascitic fluid carcinoembryonic antigen (CEA) levels >5 ng/mL or alkaline phosphatase quantities >240 units/L are fairly sensitive and specific in the detection of gut perforation.[60] Computed tomography (CT) with oral and intravenous contrast material greatly enhances the detection of intraabdominal sources of secondary peritonitis. Surgery often can be directed toward a potential source of infection identified on the basis of CT findings, rather than by a full exploratory laparotomy, which is known to be associated with high rates of mortality in certain groups of patients, such as cirrhotic patients. A large proportion of cirrhosis in patients with primary peritonitis is due to alcohol ingestion. Alcoholic hepatitis may also manifest with fever and abdominal pain, but the peripheral leukocytosis often observed with the latter does not result in an elevated ascitic fluid PMN count, which suggests concurrent primary peritonitis, if present.[61] Patients with primary peritonitis usually respond within 48 to 72 hours to appropriate antimicrobial therapy.[62] The observation of an exponential rate of decline in the number of ascitic fluid leukocytes after the initiation of antimicrobial therapy for primary peritonitis has also been found to help differentiate primary from secondary bacterial peritonitis.[63]

The finding of pneumococci in peritoneal fluid may not indicate primary peritonitis, as illustrated by a case report of appendicitis and secondary peritonitis caused by pneumococci.[64] For this reason, some surgeons have considered the differential diagnosis between appendicitis and primary peritonitis too difficult to make in children without operative examination, even when gram-positive bacteria are identified in peritoneal fluid. Paracentesis for smear and culture is indicated in all cirrhotic patients with ascites and in children with gross proteinuria and abdominal pain, regardless of whether the diagnosis of nephrotic syndrome has been established. Paracentesis is not without hazard, however, especially in patients with hemorrhagic tendencies and bowel distention. In a retrospective analysis of 242 consecutive diagnostic abdominal paracenteses in patients with liver disease and ascites, major complications were reported in 7, including perforation of the bowel with generalized peritonitis or abdominal wall abscess.[65] Fortunately, hemorrhagic complications, except in the setting of disseminated intravascular coagulation, are rare, as demonstrated in one large study,[66] despite the presence of significantly elevated international normalized ratio (INR) values and diminished platelet counts.

In patients with a subacute or chronic course of primary peritonitis, other pathogens must be considered. The diagnosis of tuberculous peritonitis usually can be made at surgery or laparoscopy and confirmed by the histologic characteristics of the peritoneal biopsy specimen and by bacteriologic examination of the peritoneal biopsy specimen and fluid. The use of polymerase chain reaction (PCR) testing of fluid and tissue samples can aid in the diagnosis of tuberculous peritonitis.[67] The diagnosis of *C. immitis* peritonitis is best established with culture of ascitic fluid. The laboratory should be apprised of this diagnostic possibility because isolation of the fungus is a biohazard.

Prognosis

The treatment of primary peritonitis has been reported to be successful in more than half of cirrhotic patients, but because of the frequency of accompanying end-stage cirrhosis, the overall mortality rate in cirrhotic adults has been 95%.[16] Subsequent studies, however, reported lower mortality rates of 70% and 57%,[19,20] and 28% and 40%, respectively, died from the primary peritonitis. Patients with the poorest prognosis were found to have renal insufficiency, hypothermia, hyperbilirubinemia, and hypoalbuminemia. The lower mortality rates in these later series can perhaps be explained by the less frequent occurrence of hepatic encephalopathy. The lowest hospitalization- and infection-related mortality rates (37.8% and 2.2%, respectively), reported later, were attributed to early diagnosis and treatment.[62] Septic shock due to primary peritonitis had an overall in-hospital mortality rate of 82%, but chance of survival is greatly improved in patients who receive earlier, adequate, and timely antimicrobial therapy.[68] However, patients with severe enough liver disease to develop spontaneous bacterial peritonitis have a poor long-term prognosis; 1- and 2-year mortality rates are 70% and 80%, respectively.[69] Therefore, liver transplantation should be considered for survivors of spontaneous bacterial peritonitis who meet other criteria for transplantation. Treatment of peritonitis caused by gram-positive organisms and of early infections has been more frequently successful than treatment of gram-negative or late infections. In patients with nephrotic disease and gram-positive infections and in patients who do not have a preterminal underlying illness, the survival rate is higher than 90%.[11]

TABLE 74.1 Primary Peritonitis: Indications for Initiation of Therapy

Temperature >37.8°C (100°F)
Abdominal pain and/or tenderness
An unexplained change in mental status
Laboratory abnormalities suggestive of infection (e.g., renal failure, acidosis, or peripheral leukocytosis)
Peritoneal fluid neutrophil count ≥250 cells/mm^3

Therapy

Primary peritonitis is managed medically unless secondary peritonitis is suspected on the basis of clinical, laboratory, or imaging findings, in which case either exploratory laparotomy or laparoscopy, or percutaneous radiologic interventions are performed. In primary peritonitis, indications for initiation of therapy are listed in Table 74.1. Delays in treatment pending culture results may negatively affect clinical outcomes. Other than in emergent situations, it is best that antibiotics not be administered until after ascitic fluid has been obtained for culture in order to optimize the chance of isolating the pathogenic organism.

Because the Gram stain is frequently negative in primary bacterial peritonitis, the initial choice of antimicrobial drug is often empirical, based on the most likely pathogens. Relatively few data exist to guide the optimal selection and dose of antibiotics for treatment of spontaneous bacterial peritonitis.[70] The antimicrobial regimen can be modified when the results of the culture and susceptibility tests are available. Cefotaxime and similar third-generation cephalosporin antibiotics (e.g., ceftriaxone) have been shown to be as efficacious as the combination of ampicillin plus an aminoglycoside for empirical therapy in primary bacterial peritonitis.[71] In addition to high rates of resolution of infection, the third-generation cephalosporins also avoid the risk of nephrotoxicity, which is sufficiently common in this group of patients to warrant the avoidance of aminoglycosides if an equally effective alternative antimicrobial regimen can be used.[20] These extended-spectrum cephalosporins may also be effective in treating patients who are suspected of being infected with a fluoroquinolone-resistant pathogen as a consequence of their having taken oral fluoroquinolone prophylaxis.[72] Other antimicrobial agents, such as β-lactam/β-lactamase combinations (e.g., piperacillin-tazobactam, ticarcillin-clavulanate, ampicillin-sulbactam) and carbapenems (e.g., imipenem, meropenem, doripenem, ertapenem), are potential alternatives.[15] The extended-spectrum fluoroquinolones (e.g., levofloxacin and moxifloxacin) may also be used in patients with contraindications to β-lactam drugs. However, these agents should be avoided if patients were previously receiving a fluoroquinolone for prophylaxis, because there is a high probability that the infecting bacteria are resistant to similar medications. Although intravenous antimicrobial therapy may be preferred, oral administration of antibiotics, such as amoxicillin-clavulanate or fluoroquinolones, may be equally efficacious in patients with uncomplicated disease,[15] assuming the prevalence of resistance to *E. coli* and other Enterobacteriaceae is not high.

Primary bacterial peritonitis caused by either *S. pneumoniae* or group A streptococci is treated best with high-dose penicillin, ceftriaxone, or cefotaxime. If the pneumococcal strain is highly resistant to these drugs, vancomycin is the preferred drug and it may be prudent to include vancomycin until sensitivities of pneumococci are ascertained. Peritonitis suspected of being caused by methicillin-sensitive *S. aureus* should be treated with a penicillinase-resistant penicillin (e.g., nafcillin) or with a first-generation cephalosporin (e.g., cefazolin); if the strain is methicillin resistant or if the patient is allergic to penicillin, vancomycin, daptomycin, telavancin, or linezolid can be used. If *Pseudomonas aeruginosa* is isolated, an antipseudomonal penicillin, ceftazidime, cefepime, ceftolozane-tazobactam (may be active against strains of multidrug-resistant *P.*

aeruginosa), ceftazidime-avibactam, aztreonam, a carbapenem (e.g., imipenem, meropenem, or doripenem), or a fluoroquinolone with good antipseudomonal activity (e.g., ciprofloxacin) could be combined with another antipseudomonal antibiotic, although use of aminoglycosides is discouraged because of nephrotoxicity.[73] More recently, multidrug resistance (mainly via extended-spectrum β-lactamase [ESBL] production) has been encountered among strains of gram-negative bacilli isolated in primary peritonitis. Although this appears to occur with greater frequency in nosocomially acquired and health care–associated cases, resistance to ceftriaxone was found in 7% of community-acquired primary peritonitis cases.[74] In this setting, a carbapenem would be the antimicrobial agent of choice.

In cases in which there is a strong clinical suspicion of primary bacterial peritonitis but all cultures are sterile, antimicrobial therapy should be continued. Clinical improvement together with a significant decline in the ascitic fluid PMN leukocyte count of greater than 25% should occur after 24 to 48 hours of antimicrobial therapy if the diagnosis is correct.[62,63,75] Likewise, a follow-up fluid analysis to document sterility of an initial positive culture and a marked decrease in PMN leukocyte count is not necessary in most patients with spontaneous bacterial peritonitis. However, a repeat paracentesis should be considered in cases in which an expected clinical response is lacking or an unusual organism is present. If the PMN leukocyte count in ascitic fluid continues to be elevated, other diagnoses should be considered. Historically, antimicrobial therapy generally was continued for 10 to 14 days if improvement was noted; however, shorter courses (5 days) of therapy have been shown to be as efficacious.[62] Longer treatment courses may be warranted and should be considered in the setting of resistant bacterial pathogens, and when the clinical response is slower than expected or when results of follow-up of ascitic fluid analysis remain significantly abnormal. The administration of intraperitoneal antimicrobials is not necessary. A meta-analysis of four controlled trials found that intravenous albumin infusion along with antibiotics resulted in a significant decrease in the incidence of acute kidney injury (8% vs. 31%), and a reduction in mortality (16% vs. 35%).[73] Renal insufficiency, as a consequence of further reduction in effective arterial blood volume with a resultant increase in activity of the renin-angiotensin-aldosterone system, occurs in about one-third of patients with primary peritonitis. Patients with ascitic fluid PMN leukocyte cell counts of at least 250 cells/mm^3 and in whom primary peritonitis is clinically suspected should receive 1.5 g albumin/kg body weight within 6 hours of detection and 1.0 g/kg on day 3. Albumin administration is also indicated when the serum creatinine is >1 mg/dL, blood urea nitrogen is >30 mg/dL, or total bilirubin is >4 mg/dL.[76] Nonselective β-blockers have been determined to significantly increase the risk of mortality and rates of hepatorenal syndrome in patients with cirrhosis who developed primary peritonitis and therefore should not be used.[77]

Patients with peritoneal fluid PMN leukocyte cell counts less than 250 cells/mm^3 and signs or symptoms of infection should receive antibiotic therapy as detailed earlier for primary peritonitis, while awaiting results of cultures, because symptomatic patients with monomicrobial nonneutrophilic bacterascites variant are prone to progress to primary peritonitis, even though at the time of the paracentesis it is not known whether the cultures will yield bacteria. Because only 15% of asymptomatic patients with monomicrobial nonneutrophilic bacterascites progress to primary peritonitis, this group of otherwise asymptomatic patients usually does not need antibiotics, and observation is appropriate. Therefore it is recommended that in these asymptomatic patients the paracentesis be repeated as soon as the first culture yields bacteria. Antibiotics are initiated only if signs or symptoms of infection develop or if the second paracentesis demonstrates neutrocytic ascites. The majority of patients with culture-negative neutrocytic peritoneal fluid (PMN count >250 cells/mm^3) have primary peritonitis. In those instances, the same empirical antimicrobial therapy should be given.

Prevention

Because of the common occurrence and high mortality of primary peritonitis in the presence of cirrhosis and ascites, prevention is a desirable strategy. This is particularly true for patients who are awaiting liver transplantation. Patients with a heightened risk of developing primary peritonitis include those with ascitic protein concentrations of less than 1 g/dL, variceal bleeding, or a prior episode of primary peritonitis. In randomized controlled trials, the use of antibiotic prophylaxis has been proven to decrease infection episodes and lower mortality rates in such individuals. Similarly, prophylaxis is recommended in patients with cirrhosis and gastrointestinal bleeding, and in those admitted to the hospital for unrelated reasons but who are known or found to have low ascitic fluid protein concentrations (Table 74.2). Short-term (7 days) inpatient intravenous ceftriaxone should be given to prevent primary peritonitis in hospitalized patients with advanced cirrhosis and gastrointestinal bleeding. This can be changed to oral double-strength trimethoprim-sulfamethoxazole, ciprofloxacin 500 mg every 12 hours, or norfloxacin 400 mg twice daily to complete the course once bleeding has ceased and the patient's condition is stable. Because active bleeding is the risk factor for infection, patients who are undergoing sclerotherapy or variceal banding to prevent bleeding do not require antibiotic prophylaxis.[78]

TABLE 74.2 Prevention and Prophylaxis of Primary Peritonitis (Cirrhotic Patients With Ascites)

INDICATION	ANTIBIOTIC REGIMEN
Variceal or gastrointestinal bleeding	Ceftriaxone 1 g IV for 7 days, can be changed to oral TMP-SMX DS or ciprofloxacin 500 mg or norfloxacin 400 mg twice daily to complete the 7-day course, once bleeding has ceased and the patient is stable
Prior episode of primary peritonitis	Oral TMP-SMX DS, or ciprofloxacin 500 mg, or norfloxacin 400 mg once daily
Ascitic fluid protein <1 g/dL	Oral TMP-SMX DS, or ciprofloxacin 500 mg, or norfloxacin 400 mg once daily
Ascitic fluid protein <1.5 g/dL with impaired renal function[a] or liver failure[b]	Oral TMP-SMX DS, or ciprofloxacin 500 mg, or norfloxacin 400 mg once daily

[a]Creatinine >1.2 mg/dL, blood urea nitrogen >25 mg/dL or serum sodium <130 mEq/L.
[b]Child-Turcotte-Pugh score >9 and bilirubin >3 mg/dL.
TMP-SMX DS, Trimethoprim-sulfamethoxazole double strength.

Patients who have survived one episode of primary peritonitis have an increased 1-year probability of another episode. A combined meta-analysis of 13 trials in which antibiotic prophylaxis was given to hospitalized patients with cirrhosis who had various risk factors for infection (i.e., low-protein ascitic fluid, gastrointestinal bleeding, and history of primary bacterial peritonitis) showed an overall decrease in mortality and a decrease in bacterial infection.[79] Subsequent meta-analyses have reached similar conclusions.[80,81] One concern with prolonged antibiotic prophylaxis is the potential selection of resistant gut bacterial flora, which can subsequently cause spontaneous infection, and a change in the flora of bacterial infections. High-risk patients who are receiving intestinal decontamination regimens are found to have a predominance of gram-positive organisms compared with the usual predominance of gram-negative organisms.[82] In randomized trials, researchers have studied both intermittent and continuous prophylaxis and found that intermittent dosing schedules pose a higher risk of promoting bacterial resistance. Currently, continuous prolonged outpatient double-strength trimethoprim-sulfamethoxazole, ciprofloxacin 500 mg, or norfloxacin 400 mg, each given once daily, are the preferred antibiotic prophylactic regimens for otherwise asymptomatic patients with a prior history of primary peritonitis. The same long-term preventive antibiotics are recommended for patients with cirrhosis and ascites with a protein concentration <1.5 g/dL, along with either impaired renal function (creatinine >1.2 mg/dL, blood urea nitrogen >25 mg/dL, or serum sodium ≤130 mEq/L) or liver failure (Child-Turcotte-Pugh score ≥9 and bilirubin >3 mg/dL) (see Table 74.2).[25,83–86] A similar approach to prevent infection in patients awaiting liver transplantation but lacking documented risk factors is often undertaken. However, randomized trials supporting this practice are lacking.

Proton pump inhibitors have been associated with increased rates of primary peritonitis and should be avoided unless clearly indicated and required.[87] Other prevention strategies include the treatment of unrelated infections to prevent potential hematogenous spread to the ascitic fluid. Diuretic therapy effectively increases the opsonic activity in the normally dilute ascitic fluid of cirrhotic patients, leading to improved antibacterial action.[88]

Secondary and Tertiary Peritonitis

Etiology

Secondary intraabdominal infection is usually caused by spillage of gastrointestinal or genitourinary microorganisms into the peritoneal cavity secondary to loss of the integrity of the mucosal barrier. It is the most common intraabdominal infection and accounts for approximately 80% to 90% of such infections. The primary intraabdominal processes that can give rise to secondary peritonitis are numerous (Table 74.3) and include diseases or injuries of the gastrointestinal or genitourinary tract, such as perforation of a peptic ulcer; traumatic perforation of the uterus, urinary bladder, stomach, or small or large bowel; spontaneous perforation associated with typhoid, tuberculous, amebic, *Strongyloides,* or cytomegalovirus ulcers in immunocompromised persons; appendicitis, diverticulitis, or intestinal neoplasms; gangrene of the bowel from strangulation, bowel obstruction, or mesenteric vascular obstruction; suppurative cholecystitis; bile peritonitis; pancreatitis; operative contamination of the peritoneum or disruption of a surgical anastomosis site; septic abortion, puerperal sepsis, postoperative uterine infection, or endometritis complicating an intrauterine device; gonococcal salpingitis or gonococcal vulvovaginitis in children; suppurative prostatitis; and rupture of an intraperitoneal or visceral abscess, such as renal or perinephric, tubo-ovarian, liver, splenic, or pancreatic abscess. Peritonitis is a major hazard of continuous ambulatory peritoneal dialysis (CAPD) used in the management of renal failure, fluid and electrolytic imbalance, and certain intoxications. Bacterial peritonitis commonly occurs secondary to the use of peritoneovenous and ventriculoperitoneal shunts.[89]

Peritoneal signs suggestive of appendicitis in immunocompromised patients (e.g., patients with acquired immunodeficiency syndrome, organ transplant recipients, patients receiving chemotherapy or corticosteroids for neoplasms, especially myelosuppressive drugs) may be caused by typhlitis, also referred to as *neutropenic enterocolitis,*[90] an inflammation of the cecum. Cecal ulceration in these patients may progress to perforation and secondary peritonitis with colonic flora.

Tertiary peritonitis has been conceptualized as a later stage in the disease, when clinical peritonitis and systemic signs of sepsis persist after treatment for primary or secondary peritonitis. Many times no organisms or low-virulence pathogens, such as enterococci (including vancomycin-resistant strains), coagulase-negative *Staphylococcal* species, Enterobacteriaceae, anaerobes, and fungi (mostly *Candida* species), are isolated from the peritoneal exudate.[9,91] This category of peritoneal infection is more common among critically ill or immunocompromised patients and is characteristically without a surgically treatable focus, following an earlier surgical intervention and source control. In health care–associated intraabdominal infections, which typically encompass tertiary peritonitis, more resistant nosocomial pathogens may also be playing a major role in the infectious process.[9] These organisms may gain access to the peritoneal cavity through contamination during operative interventions, through selection from the initial polymicrobial peritoneal inoculum by antibiotic therapy, or through translocation of bowel flora.

TABLE 74.3 Causes of Secondary Peritonitis

Distal esophagus	Boerhaave syndrome Malignancy Trauma Iatrogenic[a]
Stomach	Peptic ulcer perforation Malignancy Trauma Iatrogenic[a]
Duodenum	Peptic ulcer perforation Trauma Iatrogenic[a]
Biliary tract	Cholecystitis Stone perforation from gallbladder or common duct Malignancy Trauma Iatrogenic[a]
Pancreas	Pancreatitis (e.g., alcohol, drugs, gallstones) Trauma Iatrogenic[a]
Small bowel	Ischemic bowel Incarcerated hernia Crohn disease Malignancy Meckel diverticulum Trauma
Large bowel and appendix	Ischemic bowel Diverticulitis Malignancy Ulcerative colitis and Crohn disease Appendicitis Volvulus Trauma (mostly penetrating) Iatrogenic[a]
Uterus, salpinx, and ovaries	Pelvic inflammatory disease (e.g., salpingo-oophoritis, tubo-ovarian abscess, ovarian cyst) Trauma Malignancy Iatrogenic[a]

[a]Dehiscence of surgical anastomosis or inadvertent injury during a procedure (e.g., endoscopy).

Modified from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. *2010;50:133–164.*

Microbiologic Characteristics

Infrequently, exogenous microorganisms, such as *S. aureus, N. gonorrhoeae,* or *M. tuberculosis,* which cause infection in intraabdominal or adjacent viscera and spread to involve the peritoneum, cause secondary peritonitis. Most cases of secondary peritonitis are endogenous in origin, however, and are caused by the large number and variety of microorganisms that normally colonize mucous membranes lining certain viscera within the abdominal cavity. Characteristically, secondary peritonitis is a polymicrobial infection involving both facultative and obligate anaerobes. Although forming a continuous surface, the mucous membranes of the stomach, upper small bowel, lower small bowel, and large bowel each have characteristic microbiota in terms of type of microbial species, total number of different species, and microbial density. The vagina also has distinct microbiota. Normally, invasive activities of indigenous bacteria are controlled by the intact mucosa of the gastrointestinal tract and vagina. Disturbances in this mucosal barrier can occur as a result of spontaneous disease, trauma, or surgical operations that permit escape of indigenous bacteria and cause an infection of the peritoneum, the abdominal viscera, or the retroperitoneal space. The frequency with which various indigenous organisms are found in intraabdominal infections varies according to the site of the primary process and whether the primary process is associated with an alteration of the indigenous microbiota. Changes in the microflora may result from previous antibiotic therapy, the use of other medications (e.g., those that modify the acidity or alkalinity of gastric and intestinal secretions), and specific host factors, such as any degree of immunodeficiency. In addition, the anticipated microbiota in these infections is determined by whether the infection is community acquired or health care associated. In community-acquired intraabdominal infections, the location of the inciting event generally defines the infecting microbiota, whereas intraabdominal infections categorized as health care associated often involve nosocomially acquired pathogens specific to the diseased organ or postoperative event and at least one multidrug-resistant pathogen.[92,93] The prevalence of Enterobacteriaceae other than *E. coli,* or non–lactose-fermenting gram-negative aerobic bacilli (e.g., *Pseudomonas* species), is increasing. In addition to aerobic streptococci, health care–associated intraabdominal infections in postsurgical patients who

received prior antimicrobial therapy are more likely to involve other gram-positive cocci such as enterococci and staphylococci, some of which may be vancomycin and methicillin resistant. The risk of *Candida* species being present is also increased in these clinical settings. Over time, the bacterial species in community-acquired infections have not significantly changed. However, depending on the patient's geographic location, the antimicrobial susceptibility patterns of these microorganisms, particularly among the Enterobacteriaceae group, have significantly changed.[94] Once rare, extended-spectrum β-lactamase producing *E. coli* and *Klebsiella* species are now increasingly encountered in community-acquired intraabdominal infections.[95]

The bacteria that cause intraabdominal infections are derived from the indigenous microbiota of the gastrointestinal tract. Because gastrointestinal perforation is the most common precipitating event, knowledge of the types and quantities of the normal microflora at these various anatomic sites is key to understanding the spectrum of intraabdominal infections that may ensue.[96] The stomach normally contains 10^3 colony-forming units (CFUs) of microorganisms per milliliter in the fasting state. If bacteria are present, they consist of a few relatively more acid-resistant species or yeast made up mostly of facultative, gram-positive, salivary microorganisms, such as *Candida* spp., lactobacilli, and oral streptococci derived from oropharyngeal flora. The numbers of these organisms in stomach contents increase transiently after a meal. Gastric microbiota is more numerous and may be composed of different organisms when achlorhydria is present (e.g., from type 2 antihistamine or proton pump inhibitor medications), obstruction exists, or blood is in the stomach. Under these circumstances, gastric colonization with oropharyngeal anaerobes such as *Prevotella,* non-*fragilis Bacteroides,* and *Fusobacterium* spp., along with facultative organisms, such as viridans streptococci, microaerophilic streptococci, *Candida* spp., and lactobacilli, may greatly increase. Because of the cleansing activity of gastric acidity and rapid small bowel motility, the duodenum and proximal small bowel contain a sparse microbiota in the fasting state, mostly consisting of salivary microorganisms. In the presence of achlorhydria, intestinal obstruction, or other processes affecting intestinal motility or absorption, however, the microbiota of the small intestine is more profuse and varied. Conditions conducive to small bowel stasis include scleroderma, regional enteritis, small bowel strictures, nontropical sprue, tropical sprue, duodenal and jejunal diverticula, presence of an afferent loop of the Billroth II gastrojejunostomy, and intestinal pseudo-obstruction. Large-bowel flora has been found in the proximal small bowel of cirrhotic patients. The ileum normally contains *E. coli,* enterococci, and an equal number of microorganisms that are obligately anaerobic, such as *B. fragilis.* It is the colon, however, in which profuse microflora exist in concentrations of about $10^{11–12}$ bacteria per gram of feces, a wet sludge of practically pure bacteria. The colonic microbiota is composed predominantly of the obligate anaerobes *B. fragilis* and *Bifidobacterium* spp., which outnumber facultative microorganisms, primarily *E. coli,* by 10^3:1 to 10^4:1. Other colonic bacteria are *Streptococcus viridans* and other streptococci, enterococci, *Eubacterium* spp., *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., and *C. perfringens.* The large-bowel microbiota are relatively stable but may be altered significantly by antibiotic therapy or in patients who have been hospitalized recently or have spent time in other health care facilities.[1,97] Under these circumstances, organisms such as *P. aeruginosa* and *Acinetobacter* spp. may be commonly isolated in hospital-acquired intraabdominal infections.[93] In addition, the prevalence of multidrug-resistant gram-negative bacilli, especially those that produce ESBLs, has significantly increased.[98] The differences in microorganisms observed when the source is in the upper versus lower gastrointestinal tract may partially account for the differences in severity of septic complications after injuries or diseases along the gastrointestinal tract, with sepsis resulting from the more proximal gastrointestinal tract causing less morbidity and mortality than that seen with colonic disease processes.

With loss of the integrity of the mucosal barrier at some point along the gastrointestinal tract, a variable amount of bacteria (in terms of bacterial density and number of different species) is found in the peritoneal cavity, depending on the level of the mucosal defect and comorbid conditions. With perforation of the colon, initially a total of more than 10^{11} CFUs/mL of hundreds of different species spills into the peritoneal cavity. A simplification of the microflora occurs so that when peritoneal infection is established, only about five species are isolated from peritoneal exudate, usually three anaerobic and two aerobic species, even when care is exercised to ensure recovery of the obligate anaerobes. The obligate anaerobes isolated from clinical specimens have been found to be more oxygen tolerant and to have more identifiable virulence factors than the rest of the anaerobic microflora in the gut. The facultative anaerobes isolated also have virulence factors. *B. fragilis* is the obligate anaerobe most frequently isolated after colonic perforation, and *E. coli* is the facultative anaerobe most frequently isolated.

As would be anticipated from the nature of the gastrointestinal microbiota, anaerobes are recovered in 96% of cases of peritonitis secondary to acute appendicitis with perforation. *Prevotella melaninogenica* and anaerobic gram-positive cocci are the most frequent isolates. With the use of modern bacteriologic techniques that provide an anaerobic environment during collection, transport, and incubation, studies of the bacteriologic characteristics of intraabdominal infections[99–101] have confirmed the findings that anaerobes play a major role. Finegold[99] reported that in a series of 73 intraabdominal infections, including 16 cases of peritonitis, there were on average 4.5 isolates per case (range, 1–12 organisms), with 2.5 anaerobes and 2 aerobes or facultative organisms. The most common isolate was *E. coli,* followed by *B. fragilis* (the most common anaerobic isolate), enterococci, other *Bacteroides* spp., *Fusobacterium, C. perfringens,* other clostridia, *Peptococcus* spp., *Peptostreptococcus* spp., and *Eubacterium* spp. Similar findings were reported by Gorbach and coworkers[100] in a series of 43 patients, including 10 with peritonitis, in 93% of whom anaerobes or a mixture of anaerobes and facultative organisms were isolated, and by Swenson and colleagues[102] in a series of 64 patients, including 26 with peritonitis, in 81% of whom anaerobes were isolated. In these series, bacteremia was reported in 20% to 30% of patients. Organisms recovered from blood frequently included *B. fragilis* or *E. coli.* In a series of patients with *Bacteroides* bacteremia, 14% to 62% had a gastrointestinal source.[103] Table 74.4 lists the major bacterial organisms identified and their approximate prevalence from multiple complicated intraabdominal infection antibiotic trials.[1,2,104]

In a study of perforated appendicitis in which careful anaerobic culture techniques were used, an average of 9.4 species of anaerobes were isolated from each patient.[105] *Bilophila wadsworthia,* an anaerobic gram-negative bacillus, was the fourth most common obligate anaerobe isolated and was found in one-third of patients with gangrenous appendicitis and half of patients with perforated appendicitis.[106]

Relatively antibiotic-resistant organisms, such as *Candida* spp., enterococci, *Enterobacter* spp., *Serratia* spp., *Acinetobacter* spp., and *P. aeruginosa,* are isolated more frequently from patients whose intraabdominal infection developed while they were in the hospital, after they received broad-spectrum antimicrobial agents.[107,108] Reported isolation rates for these uncommon intraabdominal pathogens vary; one large study found that nonfermenting gram-negative bacteria (*P. aeruginosa, Stenotrophomonas maltophilia,* and *Acinetobacter baumannii*) accounted for less than 6% of all intraabdominal infections, and a second study found *P. aeruginosa* in about 9% of patients diagnosed with secondary peritonitis.[109,110] Several studies have revealed, however, that *P. aeruginosa* makes up a more significant portion of the aerobic isolates in community-acquired intraabdominal infections[111,112] than had been noted previously. Whether or not the isolation of *P. aeruginosa* represents contamination rather than a true pathogen is subject to question, with one study demonstrating that coverage of *Pseudomonas* did not add to higher rates of clinical success.[110]

Monomicrobial infections with microorganisms that have relatively low pathogenicity, such as *Candida* spp., enterococci, or coagulase-negative staphylococci, have also been observed in what was thought to be new-onset peritonitis in patients with severely impaired defenses.[113] Penetrating injuries to the liver and spleen are followed by infection only rarely because of the usual sterility of these organs.[114]

Quantitative studies[115,116] of sexually active women of childbearing age have revealed that the predominant vaginal microbiota are composed of five to seven different microorganisms and that anaerobes are approximately 10 times more numerous than facultative organisms. There are about 10^8 to 10^9 CFUs of anaerobes and about 10^7 to 10^8 CFUs of facultative organisms per milliliter of vaginal secretions. The most

TABLE 74.4 Organisms That Cause Complicated Intraabdominal Infections

ORGANISM	PATIENTS (%)
Aerobes only[a]	17
Anaerobes only[a]	1
Anaerobes + aerobes[a]	82
Facultative and Aerobic Gram-Negative Bacilli[b]	
Escherichia coli	71
Klebsiella spp.	14
Pseudomonas aeruginosa	14
Proteus mirabilis	5
Enterobacter spp.	5
Anaerobic[b]	
Bacteroides fragilis	35
Other *Bacteroides* spp.	71
Clostridium spp.	29
Prevotella spp.	12
Peptostreptococcus spp.	17
Fusobacterium spp.	9
Eubacterium spp.	17
Gram-Positive Aerobic Cocci[b]	
Streptococcus spp.	38
Enterococcus faecalis	12
Enterococcus faecium	3
Enterococcus spp.	8
Staphylococcus aureus	4

[a]*From Stone HH, Strom PR, Fabian TC, et al. Third-generation cephalosporins for polymicrobial surgical sepsis.* Arch Surg. *1983;118:193–200.*
[b]*Modified from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America.* Clin Infect Dis. *2010;50:133–164.*

frequent isolates in titers of 10^5 per milliliter or more are obligate or facultative anaerobic lactobacilli, streptococci, anaerobic gram-positive cocci, Bacteroidaceae other than *B. fragilis* (e.g., *P. melaninogenica, Prevotella bivia, Prevotella ruminicola*), and a group of unidentified catalase-negative facultative bacilli. Diphtheroids and *Staphylococcus epidermidis* also have been found to be frequent vaginal isolates. When specifically looked for, *Gardnerella vaginalis* in high counts has also been found to be only slightly less common than lactobacilli in the vaginal secretions of healthy women.[115,116]

Colonic organisms, such as *B. fragilis,* Enterobacteriaceae, and enterococci, are found rarely as predominant components of the normal vaginal microbiota and probably proliferate at this site only under exceptional circumstances. These organisms tend to appear in vaginal secretions in the immediate postoperative period after vaginal operations, and *C. perfringens* is found more frequently in vaginal secretions after difficult labor or abortion. *Bacteroides* spp. and anaerobic gram-positive cocci are infrequent commensals in the vagina of healthy women prenatally, whereas during the puerperium these organisms are found to be more prevalent in women with postpartum endometritis than in noninfected women.[117] Factors favoring colonization by these anaerobes after surgery and in the puerperium are unknown but are possibly related to blood or necrotic tissue, which provides the reduced, enriched environment required by these anaerobes.

Sequential sampling of vaginal secretions during the menstrual cycle reveals constant levels of anaerobes, although recovery of specific organisms varies from specimen to specimen in each individual woman. In contrast, levels of facultative organisms decrease 100-fold in the premenstrual week. This variation in microbiota may reflect cyclic fluctuation in the vaginal environment caused by changes in hormonal activity during the menstrual cycle. Because the vaginal microbiota vary under certain conditions, and members of these flora have differing pathogenicity, the frequency of indigenous intraabdominal infections of gynecologic origin and the types of pathogens involved vary accordingly. The frequency of vaginal colonization with group B streptococci increases during pregnancy, and infections caused by these organisms are relatively common in the postpartum period. In addition, in women with trichomoniasis, *Bacteroides* spp. may be found more often in vaginal secretions.[116] Postpartum infection, presumably caused by anaerobes, has been reported to be more common in women who had trichomoniasis during pregnancy.[118]

The bacteriologic characteristics of intraabdominal infections that complicate infections of the female genital tract are similar to those of secondary peritonitis from a gastrointestinal source except for the occurrence of *N. gonorrhoeae* in cul-de-sac aspirates. According to data compiled by Swenson and associates,[119] Thadepalli and coworkers,[120] and Chow and colleagues,[121] anaerobes were found in 72% of 200 gynecologic infections. Anaerobes were especially frequent (92%) in closed space infections, such as tubo-ovarian and pelvic abscesses. *Bacteroides* spp., particularly *B. fragilis* and *P. melaninogenica,* and anaerobic gram-positive cocci were the most frequently isolated anaerobes. *E. coli* and streptococci were the most prevalent facultative organisms. Bacteriologic studies have shown the presence of anaerobes, usually gram-positive cocci in cul-de-sac aspirates, in most patients, even those with acute salpingitis, despite the recovery of gonococci from the endocervix.[122] The data are interpreted as supporting the concept of superinfection with anaerobes late in the course of this disease, after initial infection with *N. gonorrhoeae.*[123] In children, gonococcal peritonitis has been reported only rarely with gonococcal vulvovaginitis.[124]

Intraperitoneal rupture has been reported in 10% of cases of amebic liver abscess, and it may cause acute generalized peritonitis or, less commonly, a localized intraperitoneal abscess, with a mortality rate of about 18%.[125] Perforation of the colon with bacterial peritonitis resulting from fulminant amebic colitis is also unusual but often fatal. Similarly, *Strongyloides stercoralis* infestation of the small bowel may, in rare cases, cause fatal peritonitis, with or without concurrent bacterial contamination.[126] Intestinal perforation complicating penetrating cytomegalovirus enterocolitis has been described as a cause of an acute abdomen in these patients. *Candida* spp. have been isolated from the abdominal fluid of patients undergoing peritoneal dialysis, as have *S. aureus,* Enterobacteriaceae, and *P. aeruginosa.*[127] *Candida* peritonitis may also be observed as a complication of gastrointestinal surgery or in perforation of a viscus,[128] and its occurrence is related to numerous factors that increase the rate of colonization of *Candida* organisms in the gastrointestinal tract. These factors include immunosuppression, prolonged hospitalization, and antimicrobial or antacid therapy. *Candida* spp. are most commonly isolated from the peritoneum after perforation of a gastric or duodenal peptic ulcer or after spillage of colonic contents into the peritoneum as a result of trauma, mesenteric artery occlusion, or dehiscence of a surgical anastomosis.

Pathogenesis

The virulence of the bacteria that cause peritonitis is enhanced when certain microorganisms are either combined intraperitoneally with substances such as mucus, enzymes, or hemoglobin or are combined with certain other microorganisms. Chemical peritonitis can be produced by escape of bile or of gastric or pancreatic secretions into the peritoneal cavity. When gastric acid escapes into the peritoneal cavity, there is an outpouring of serum protein and electrolytes from the blood into the peritoneal cavity. The acidity is neutralized quickly by these buffers and by diffusion of hydrogen ions into the body fluids. Widespread necrosis may result from enzymatic digestion after intraperitoneal spillage of potent pancreatic enzymes. Escape of bile into the peritoneal cavity is generally considered to be a grave, often fatal situation. The severity of peritonitis after escape of these intestinal secretions results in subsequent bacterial peritonitis. In a dog model with experimentally produced partial biliary diversion into the peritoneal cavity, fatal effects were reduced by oral nonabsorbable or parenteral antibiotics.[129] Bacteria may enter

the peritoneal cavity with contaminated intestinal secretions through perforations in the gastrointestinal wall or by migration through the wall of the intact gastrointestinal tract in response to irritation of the serosal surface by bile and possibly other intestinal tract secretions.

Establishment of an anaerobic infection requires an environment in which the oxygen tension is low, the oxidation-reduction potential is low, and abundant nutrients are available to support anaerobic metabolism. Obligate anaerobes are sensitive to oxygen in the molecular form and to bound oxygen, as in organic peroxides. Survival and growth of anaerobes also depend on the oxidation-reduction potential (i.e., the oxidizing capacity of the environment). Most pathogenic anaerobes require a negative potential of at least −150 mV. Low oxidation-reduction potentials are thought to occur in many abscesses, and oxidation-reduction potentials of −150 mV or less are measured in abscesses from which anaerobes are recovered.[130] Some anaerobic organisms have additional requirements, such as vitamin K, arginine, serum, blood pigments, or bile, before they can grow. These requirements are usually met by tissue devitalized as a consequence of ischemia, trauma, or neoplastic growth. When proper conditions are obtained, anaerobic organisms can achieve doubling rates equivalent to rates seen with aerobic enteric bacilli. In vivo, the rapidly expanding bacterial and inflammatory cell mass, frequently accompanied by gas production, can interrupt the blood supply to the immediately surrounding tissue and cause further tissue necrosis.

Gram-negative anaerobic cocci and bacilli (including *B. fragilis* and *P. melaninogenica*) possess endotoxins, although with much weaker biologic activity in comparison with endotoxins extracted from their aerobic counterparts, and they have low or absent 2-keto-3-deoxyoctanoate content. In addition, certain anaerobes elaborate collagenase, other proteolytic enzymes, and deoxyribonuclease. Certain Bacteroidaceae are capable of degrading heparin, a capability that may be responsible for the suppurative thrombophlebitis frequently seen in infections caused by these microorganisms. These factors tend to provide more areas well adapted to the growth requirements of the anaerobe; as a result, the infection progresses.

In addition, anaerobes may be resistant to host defenses. PMN leukocytes have been shown to have bactericidal activity under aerobic and anaerobic conditions against several anaerobic species, including *B. fragilis,* presumably by mechanisms other than those dependent on the superoxide anion O_2^- or H_2O_2. However, Keusch and Douglas[131] found that granulocytic killing of *C. perfringens* was impaired under anaerobic conditions. Also, the capsule demonstrated on *B. fragilis* and *Porphyromonas asaccharolytica* (formerly *Bacteroides melaninogenicus* subsp. *asaccharolyticus*) might protect the organisms from phagocytosis and favor abscess formation.[132] Some anaerobes, especially *B. fragilis,* may be resistant to the normal bactericidal activity of serum.

Many anaerobic infections seem to be synergistic. Although it is probable that most bacteria isolated in mixed infections are nonpathogenic by themselves, their presence nevertheless may be essential for the pathogenicity of the bacterial mixture. These examples of bacterial synergism in infection were shown in periodontal infection by Socransky and Gibbons[133] and in peritonitis by Altemeier.[134]

Facultative organisms in mixed infections may be essential because they provide a sufficiently reduced environment for the growth of obligate anaerobic organisms. Another mechanism of bacterial synergy is the generation of a substance by one organism that is essential for the growth of another (e.g., the production of vitamin K, a required growth factor for *P. melaninogenica,* by diphtheroids). Anaerobes such as *Bacteroides* spp. also have shown the ability to protect aerobic bacteria from phagocytic killing[135] and from otherwise effective antibiotic therapy (e.g., via β-lactamase production).[136]

In addition, each component of the pathogenic mixture may contribute in different ways to the clinical picture. In a series of experiments, Weinstein and coworkers[137] clarified the sequence of events that occurs after contamination of the peritoneum with fecal flora. In this model, after implantation of fecal contents intraperitoneally into rats, Onderdonk and associates[138] observed that *E. coli* initially predominated in the peritoneal exudate. Bacteremia, caused by *E. coli* during this phase, was uniformly present and frequently fatal. Rats that survived developed indolent intraabdominal abscesses in which *B. fragilis* predominated. Elimination of *E. coli* by early administration of gentamicin reduced early mortality rates but did not prevent late intraabdominal abscess caused by obligate anaerobes; elimination of obligate anaerobes with clindamycin did not prevent early mortality from *E. coli* bacteremia, but it did reduce late abscess formation in survivors. These findings indicate that although *E. coli* is responsible for early mortality, *B. fragilis,* in concert with *E. coli* and perhaps other microorganisms (e.g., enterococci),[139] is responsible for late intraperitoneal abscess formation. This synergy between obligate and facultative anaerobes has long been recognized in mixed infections.[140] Studies in animal models of intraperitoneal infection have also shown that bacterial interactions with host components, specifically activation of IL-17–producing $CD4^+$ T lymphocytes by constituents of abscess-inducing bacteria such as *B. fragilis,* are necessary for abscess formation.[141]

Pathophysiologic Responses

Whatever the initiating cause of peritonitis, a similar series of reactions takes place locally and systemically.

Local Response

The local inflammatory response of the peritoneum is similar to that in other tissues, but the peritoneal lining presents a large exudative and absorptive surface. At sites of irritation, there is an outpouring of fluid into the peritoneal cavity that, in contrast to normal serous fluid, has a high protein content (>3 g/dL) and many cells, primarily PMN leukocytes, that phagocytose and kill organisms. The exudate contains fibrinogen that polymerizes, and plaques of fibrinous exudate form on the inflamed peritoneal surfaces. This exudate glues together adjacent bowel, mesentery, and particularly omentum. Localization of the inflammatory process is aided further by inhibition of motility in involved intestinal loops. Experiments have demonstrated that radiopaque medium injected intraperitoneally at one locus spreads over much of the greater peritoneal sac within a short time. The extent and rate of intraperitoneal spread of contamination depend on the volume and nature of the exudate and on the effectiveness of the localizing processes.

If peritoneal defenses aided by appropriate supportive measures control the inflammatory process, the disease may resolve spontaneously. A second possible outcome is a confined abscess. A third course results when the peritoneal and systemic defense mechanisms are unable to localize the inflammation, which progresses to spreading diffuse peritonitis. Factors favoring spread of the inflammatory process are (1) greater virulence of bacteria, (2) greater extent and duration of contamination, and (3) impaired host defenses.

The cytokine response in peritonitis has been the subject of excellent reviews.[142,143] Many of the local abdominal and systemic manifestations of peritonitis undoubtedly are mediated by cytokines, including TNF-α, IL-1, IL-6, and IFN-γ. Cytokines appear in the peritoneal exudate to a much greater extent than in systemic circulation of patients with peritonitis.[144] These cytokines are produced by macrophages and other host cells in response to bacteria or bacterial products, such as endotoxin, and by tissues traumatized during abdominal operative procedures.

Cytokine responses have been studied in the peritoneal exudate in experimental animal models of peritonitis,[51] in patients with spontaneous bacterial peritonitis,[145] in patients undergoing CAPD,[146] and in patients with severe secondary bacterial peritonitis who were undergoing planned relaparotomy.[147] Anti-TNF antibody failed to prevent death[148] and failed to reduce serum levels of IL-1 and IL-6 in an experimental model of peritonitis.[149] In contrast, in this model, antiendotoxin antibodies were found to prevent death[150] and to reduce bacterial numbers in the peritoneal exudates and serum levels of TNF, IL-1, and IL-6. Anti-IFN-γ antibodies also afforded a protective effect in this model of experimental peritonitis and after intravenous injection of endotoxin.[151]

Systemic Response

Peritonitis leads to changes not only locally in the peritoneal cavity but also throughout the body.

Gastrointestinal. Peritonitis begins with hypermotility and is followed by paralysis of the bowel. Accumulation of fluid and electrolytes in the lumen of the adynamic bowel continues until distention is sufficient to inhibit capillary inflow and secretion ceases.

Cardiovascular. Because of the large surface area of the peritoneum, shifts of fluid into the peritoneal cavity, combined with fluid shifts into the bowel lumen, can produce a profound decrease in circulating blood volume and elevation of the hematocrit. Fluid and electrolyte loss is exaggerated further by coexistent fever, vomiting, diarrhea, and loss of aspirated gastrointestinal fluid. As the process continues, the decreased venous return to the right side of the heart leads to a decrease in cardiac output, with resulting hypotension. Usually there is evidence of increased adrenergic activity, such as sweating, tachycardia, and cutaneous vasoconstriction (i.e., cold, moist skin and mottled, cyanotic extremities).

With adequate replacement of blood volume, cardiac output may be maintained above normal. Cardiac output of two or three times normal may be necessary to satisfy the increased metabolic needs of the body in the presence of infection. Failure to sustain increased cardiac output results in progressive lactic acidosis, oliguria, hypotension, and ultimately death if the infection cannot be controlled.

Respiratory. The intraperitoneal inflammation results in relatively high and fixed diaphragms and considerable pain on respiration. This condition results in basilar atelectasis with intrapulmonary shunting of blood. Satisfactory compensation is possible only if the increase in energy demands does not exceed the respiratory reserve. Heavy cigarette smoking, chronic bronchitis, emphysema, and obesity compound the problem. With decompensation in respiratory function, hypoxemia is accompanied first by hypocapnia (respiratory alkalosis) and later by hypercapnia (respiratory acidosis). In some patients, pulmonary edema develops, not because of left ventricular failure but perhaps because of increased pulmonary capillary leakage as a consequence of hypoalbuminemia or direct effects of bacterial toxins (adult respiratory distress syndrome). In these patients, progressive hypoxemia develops with decreasing pulmonary compliance. This condition necessitates volume-cycled ventilatory assistance with increasingly higher concentrations of inspired oxygen and positive end-expiratory pressure.

Renal. Low renal perfusion may be followed by acute tubular necrosis and progressive azotemia.

Metabolic. The excretion of cortisol is increased during the first few days of peritonitis and subsequently returns to normal. The increased energy demands of infection rapidly deplete body stores of glycogen; this leads to catabolism of protein (muscle) and fat, which accounts for the rapid weight loss of severely infected patients. Prolonged intra-abdominal infection is associated with extreme wasting. Heat production eventually may fail, and then body temperature decreases. Exhaustion and death may ensue.

Clinical Manifestations

Symptoms

The early manifestations of peritonitis that results from disease of abdominal viscera are frequently those of the primary disease process. Moderately severe abdominal pain is almost always the predominant symptom. Any motion, even respiration, aggravates the pain. The progression of abdominal pain is a function of the rate of dissemination of the material producing the pain stimulus. Rupture of a peptic ulcer with massive spillage of gastric contents produces severe epigastric pain that within minutes may spread to involve the entire abdomen. In contrast, the spread of pain from a lesion such as a ruptured appendix is much more gradual. Decreased intensity and extent of pain with time usually suggest localization of the inflammatory process.

Anorexia, nausea, and vomiting commonly accompany abdominal pain. Patients may also complain of feverishness, sometimes with chill, thirst, scanty urination, inability to pass feces or flatus, and abdominal distention.

The formation and progression of an intraperitoneal abscess are often gradual. The patient who seemed to be recovering from peritonitis or an abdominal operation stops improving, fever returns, and localizing symptoms may develop.

Physical Findings

Patients with peritonitis characteristically lie quietly in bed, supine, with the knees flexed and with frequent limited intercostal respirations because any motion intensifies the abdominal pain. The patient is alert, restless, and irritable early in the course but later may become apathetic or delirious.

Body temperatures may reach 42°C. A subnormal temperature of about 35°C is often present in the early stages of chemical peritonitis. This is a grave sign late in the course in patients with continuing intraabdominal sepsis or septic shock.

Increasing tachycardia with weak, thready peripheral pulses reflects decreased effective blood volume. The blood pressure is maintained within normal limits early in the disease process. As peritonitis progresses, the blood pressure decreases to shock levels. Respiration is increasingly rapid and shallow.

Marked abdominal tenderness to palpation is present, usually maximally over the organ in which the process originated. Direct and referred rebound tenderness signifies parietal peritoneal irritation. This finding is sometimes more accurate than direct palpation in locating the point of maximal tenderness and delineating the extent of peritoneal irritation.

Muscular rigidity of the abdominal wall is produced by voluntary guarding and reflex muscular spasm. Hyperresonance caused by gaseous intestinal distention can usually be demonstrated with percussion. Pneumoperitoneum from a ruptured hollow viscus may produce decreased liver dullness to percussion. Bowel sounds, initially hypoactive, later disappear. Rectal and vaginal examination may reveal tenderness and the presence of a pelvic abscess and may indicate a primary focus in the female pelvic organs.

Abdominal pain and muscle spasm may be deceptively absent in some patients. Patients with lax abdominal musculature (e.g., patients in the postpartum period, patients with ascites caused by cirrhosis, patients with marked cachexia) may not have abdominal rigidity. Similarly, patients who are in shock, who are receiving glucocorticosteroid therapy, or in whom loculated intraabdominal abscesses are not in contact with the anterior abdominal wall (e.g., subphrenic, lesser sac, pelvic abscesses) may not exhibit marked abdominal pain and spasm. Absence of bowel sounds may be the only manifestation of peritonitis in these patients, and a high index of suspicion is necessary.

Diagnostic Studies

The differential diagnosis in patients with symptoms and signs of peritonitis includes pneumonia, sickle cell anemia, herpes zoster, diabetic ketoacidosis, tabes dorsalis, porphyria, familial Mediterranean fever, plumbism, systemic lupus erythematosus, and uremia. Routine laboratory studies include a complete blood count, serum chemistry profile, liver profile, coagulation studies, urinalysis, and amylase and lipase determinations. If an ectopic pregnancy is suspected, a urinary β-human chorionic gonadotropin (hCG) determination will be necessary. A peripheral blood leukocyte count of more than 11,000 cells/μL is usual in the majority of patients with acute peritonitis; the differential count exhibits PMN predominance and a moderate to marked shift to the left. Reliance on the significance of the total leukocyte count may be misleading, however. Massive peritoneal inflammation can mobilize leukocytes into the diseased area; there may be fewer than 5000 leukocytes/mL in the circulating blood, but the differential smear in this situation may show an extreme shift to immature PMN forms.

Hemoconcentration and dehydration are reflected by increased hematocrit and blood urea nitrogen values. Patients with severe sepsis who have disseminated intravascular coagulopathy (DIC) may have thrombocytopenia and elevated prothrombin time (PT), partial thromboplastin time (PTT), or D-dimer concentration. Blood chemistries may reveal dehydration, azotemia, and acidosis. Hyperglycemia and glycosuria are usually not present in peritonitis but may be present in diabetic acidosis and acute pancreatitis, which can manifest with signs suggestive of peritonitis. Hematuria and pyuria without bacteriuria may reflect intraabdominal inflammatory disease, such as appendicitis adjacent to the urinary tract. Levels of serum amylase and lipase may be elevated in peritonitis from almost any cause, but levels are very high (greater than three times the upper limit of normal for either enzyme) only in acute pancreatitis. Serum amylase and lipase levels may be elevated in the absence of pancreatitis because they can be caused by transmural absorption in intestinal infarction and transperitoneal absorption with perforated viscus and peritonitis. Hyponatremia may occur in patients

given water to replace isotonic fluid losses, but it is also characteristic of porphyria. Metabolic and respiratory acidosis is present in severe and late peritonitis.

Supine, upright, and lateral decubitus radiographs of the abdomen may reveal distention of the small intestine and the colon, with adynamic loops of bowel or features of mechanical intestinal obstruction, volvulus, intussusception, or vascular occlusion. Inflammatory exudate and edema of the intestinal wall produce a widening of the space between adjacent loops. Peritoneal fat lines and psoas shadows may be obliterated. Free air may be visible if a viscus is ruptured. CT scans are frequently obtained as initial studies in many centers and provide superior detail of intra-abdominal processes. Chest radiographs always should be obtained to investigate whether a pulmonary or thoracic problem is the cause of abdominal distress. The presence of air beneath the diaphragm may be defined best in these images. Trapped gas with a fluid level or mottling caused by gas may be visible in intraperitoneal or visceral abscesses. Calcification in the gallbladder or other organs may also be noted on radiographs.

Ultrasonography is frequently the initial step in evaluating intra-abdominal sepsis, especially for detecting processes in the right upper quadrant, retroperitoneum, and pelvis.[152] Dilated air-filled loops of bowel, obesity, overlying lungs, bandages, wounds, drains, and ostomies can interfere with the quality of ultrasound images. CT of the entire abdomen and pelvis, with oral and intravenous contrast agents, has become invaluable for evaluating patients with a suspected intraabdominal infection.[153] CT has frequently replaced exploratory laparotomy for this purpose. CT can facilitate detection of lesions outside the suspected area on the basis of clinical findings and guidance of percutaneous drainage of peritoneal fluid or abscesses. Although CT is more costly than ultrasonography, it is the preferred initial study except when the lesion is suspected to be in the right upper quadrant, retroperitoneum, or pelvis.[152,154] Ultrasonography is also more operator dependent than is CT, and abdominal tenderness may preclude the use of the external pressure necessary to visualize the intraabdominal contents adequately. Magnetic resonance imaging (MRI) examination may be particularly useful if additional detail of soft tissue characteristics is necessary or for provision of a three-dimensional depiction of a lesion. It is particularly sensitive for investigation of pancreatic, hepatic, or adrenal disease.[155] Laparoscopic evaluation of patients with suspected secondary peritonitis has also been reported to be useful.[156,157]

Needle aspiration of the peritoneal cavity is often helpful. If no fluid can be aspirated, peritoneal lavage with Ringer's lactate solution should be done to obtain fluid for examination. In performing a paracentesis, the operator should avoid the region of abdominal scars, where bowel may be adherent to the underside of the scar. The aspirate is examined grossly for content of blood, pus, bile, or digested fat; chemically for amylase content; and microscopically, with Gram staining, for bacteria. In lower-risk community-acquired infections resulting from processes such as perforated appendicitis, Gram staining and culturing of samples have not been routinely recommended because the encountered flora have generally been susceptible to recommended antibiotic treatment regimens with expected good treatment responses. However, increases in multidrug-resistant aerobic bacilli isolates from community-acquired infections, as seen with *E. coli* strains insensitive to extended-spectrum β-lactam antibiotics and to fluoroquinolones, have hindered the ability to reliably predict the susceptibility of isolates on the basis of knowledge of their presence alone. For other intraabdominal infections, particularly those involving the colon and health care–associated cases, failure rates are substantially higher if empirical therapy is not active against any identified isolate. Therefore, representative specimens collected from the intraabdominal focus of infection should be processed appropriately to best identify the aerobic and anaerobic bacteria present. Furthermore, Gram staining may be of value in these cases in defining the need for specific therapy for possible presence of methicillin-resistant gram-positive organisms.[158] Blood cultures have not proved clinically relevant in community-acquired infections, but they may add diagnostic information in health care–associated and tertiary peritoneal infections. A positive finding of paracentesis is meaningful; a dry or negative finding of paracentesis is of little significance. It is important to exercise caution in interpreting the relevance of bacterial isolates obtained from nonsterile sites including chronic drains or fistulas, especially when collected after prolonged periods of antibiotic exposure. Isolates obtained in this fashion generally represent colonization, demonstrate increased resistance profiles, and in the majority of cases are of no clinical importance. Guidance for the paracentesis may be obtained through ultrasonography or CT.

Prognosis

Survival of a patient with secondary peritonitis depends on many factors, including the age of the patient, nutritional status, albumin levels, comorbid conditions, the presence of malignancy, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the duration of peritoneal contamination and time to initial intervention, the presence of foreign material (e.g., bile or pancreatic secretions, barium), the primary intraabdominal process and ability to achieve adequate débridement or control of the source of infection, the microorganisms involved, and whether the infection was community or health care acquired.[159–161] Patients with community-acquired peritonitis have been further stratified into lower- and higher-risk categories. Low-risk patients admitted from the community have less than a 10% to 20% incidence of suboptimal outcomes and lower rates of death.[162,163] The more organisms present in peritoneal exudate, the worse the prognosis is, although there appears to be no correlation between severity of infection and the presence of any particular organism. However, involvement with resistant or opportunistic bacterial pathogens that are more likely to occur in health care–acquired or postoperative infections has been determined to be an independent risk factor leading to less favorable outcomes.[164] Individuals who have been hospitalized, resided in a skilled nursing or other long-term care facility, underwent home infusion therapy or wound care, underwent dialysis within the previous 30 days, or received ≥5 days of broad-spectrum antimicrobial therapy during the preceding 90 days are included in the high-risk category as having a greater potential for harboring antibiotic-resistant pathogens.[108,165] Mortality increases with more distal gastrointestinal sources of contamination.[166] In pediatric patients, because of the relatively small omentum, the walling-off process is less effective and diffuse peritonitis occurs more frequently than in adults. In elderly patients, preexisting conditions, such as emphysema, diabetes, or cardiovascular disease, reduce the capacity to meet the demands on the cardiovascular, respiratory, and renal systems during this period of intense metabolic activity. Mortality rates range from 3.5% among patients with early infection caused by penetrating abdominal trauma to more than 60% among patients with established intraabdominal infection and secondary organ failure.[167] Persistent peritoneal contamination; leakage of pancreatic enzymes; septicemia; fluid and electrolyte abnormalities; pneumonia; and cardiovascular, renal, and respiratory failure are the principal causes of death.

With a disease process that has widely varying mortality rates, the ability to predict outcome and stratify severity of disease is important for clinical decision making and for ensuring comparability in evaluating different management strategies with surgical protocols or antimicrobial agents.[168] Outcome has been found to be dependent mainly on host-related phenotypic and physiologic risk factors (e.g., preoperative nutritional status, organ impairment, severity of the patient's systemic response, and the patient's premorbid physiologic reserves, as predicted with the APACHE II scoring system),[169] rather than on type and source of the infection.[170] The Mannheim Peritonitis Index (MPI) is a simple, disease-specific, and easily used scoring system developed to predict the individual prognosis of patients with secondary peritonitis. By assigning weighted points to eight easily determined and simple clinical parameters (age, sex, organ failure, malignancy, preoperative duration of peritonitis >24 hours, origin of sepsis not colonic, diffuse generalized peritonitis, and character of exudate), the MPI score can accurately predict mortality and assist in allocating the intensity of medical and surgical management.[171]

Death from intraabdominal infection, especially when the tertiary phase is reached, is thought to result from an exaggerated, uncontrolled cytokine release that is unresponsive to all therapeutic attempts.[172] This cytokine release has led to the use of endotoxin and cytokine levels in circulation to predict outcome. The magnitude of levels of TNF-α and IL-6 in circulation in patients with peritonitis has not been related invariably to prognosis[173]; however, determination of cytokine levels in

the peritoneal exudate, rather than in blood, has been suggested to reflect better the severity of the compartmentalized peritoneal infection and to predict outcome.[147]

Therapy

Antimicrobial Therapy

Medical management includes use of antimicrobial therapy and supportive measures to maintain vital functions (e.g., improve or maintain circulation, nutrition, and oxygenation to vital organs). The clinical efficacy of immunomodulators, such as anti-TNF-α antibodies, anti-endotoxin antibodies, and IL-1 receptor antagonists, is still unproven. Recombinant human activated protein C (drotrecogin alfa), when used in the treatment of severe sepsis, had been previously demonstrated to reduce the relative risk for mortality.[174] In the subgroup of patients in the original trial who had undergone a surgical procedure and developed severe sepsis of abdominal origin, further analysis revealed an absolute reduction in risk of mortality that was still statistically significant among patients who had received active medication.[175] The greatest benefit was observed in patients with an APACHE II score of 25 points or higher (also see Chapter 75). However, in the fall of 2011, the drug manufacturer, Eli Lilly and Co., voluntarily withdrew this medication from the market in the wake of the release of the PROWESS-SHOCK trial,[176] which found no statistically significant reduction in mortality in patients treated with the sepsis drug compared with placebo.

Secondary peritonitis is typically polymicrobial, and the pathogens in most cases are derived from the gastrointestinal tract, even in patients with a primary gynecologic process. Typically, the facultative microorganisms are *E. coli, Klebsiella* or *Enterobacter* spp., *Proteus* spp., and enterococci, and the obligate anaerobes are *B. fragilis, P. melaninogenica, Peptococcus* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., *Eubacterium lentum,* and *Clostridium* spp. Less commonly isolated pathogens include *S. aureus, P. aeruginosa,* and *Candida* spp.

It is extremely difficult to assess the role of antimicrobial therapy in the outcome of infection caused by anaerobes or by a mixture of anaerobes and facultative microorganisms. Dramatic response to surgical drainage and débridement alone often occurs when infection is localized. Nevertheless, appropriate antimicrobial therapy has been shown to reduce mortality significantly among patients with bacteremic infections caused by Bacteroidaceae or Enterobacteriaceae.[1,103] Antimicrobial drugs are expected to control bacteremia and early metastatic foci of infection, to reduce suppurative complications if the drugs are given early, and to prevent local spread of existing infection. When suppuration has occurred, it may be difficult to cure the infection if antimicrobial drugs are used without drainage; also, antimicrobial drugs used alone may mask some of the clinical manifestations of abscess formation. Some intraabdominal abscesses can, however, be treated successfully with antibiotics alone.[177]

Antimicrobial agents must penetrate to the site of infection in concentrations that are sufficient to overcome the effects of a high bacterial density, the metabolic inactivity and slow growth rate of probably more than 90% of the bacterial inoculum, low pH, low redox potential, necrotic tissue, and bacterial products that may lower the drug's activity. Aminoglycosides and clindamycin are less active at acid pH, aminoglycosides are less active at low redox potentials, and β-lactams are less active against high bacterial densities.

Although the results of many antimicrobial trials for the treatment of intraabdominal infections have been published, caution must be exercised in interpreting these studies because of the possibility of inadequate study design and analysis of data.[178,179] Some of the variables that must be considered are differences in patient populations, types and severity of underlying illnesses, community-acquired versus hospital-acquired infection, and the pathogens isolated. Table 74.5 lists many of the antimicrobial regimens that may be recommended alone or in combination as initial treatment for intraabdominal infections; this list is divided by agents that should be adequate for mild-to-moderate infections and those more appropriate for infections of higher severity. The designation "high risk" describes patients with increased likelihood of treatment failure and a greater potential severity of infection according to clinical assessment criteria.[161] Such patients include those with anatomically unfavorable infections or health care–related infections.[1]

TABLE 74.5 Recommended Agents for Treatment of Complicated Intraabdominal Infections

TYPE OF THERAPY[a]	FOR MILD TO MODERATELY SEVERE INFECTIONS[b]	FOR HIGH-RISK OR HIGHLY SEVERE COMMUNITY-ACQUIRED, HEALTH CARE–ASSOCIATED, AND TERTIARY INFECTIONS[c]
Single Agent		
β-Lactam/β-lactamase inhibitor combinations	Ticarcillin-clavulanic acid Piperacillin-tazobactam	Piperacillin-tazobactam[d]
Fluoroquinolone[e]	Moxifloxacin[f]	Moxifloxacin[f]
Carbapenems	Ertapenem	Imipenem-cilastatin[d] or meropenem or doripenem or meropenem-vaborbactam
Glycylcyclines	Tigecycline[f]	Tigecycline[f]
Fluorocycline	Eravacycline	Eravacycline
Combination Therapy		
Cephalosporin based	Cefazolin, cefuroxime, cefotaxime, ceftriaxone *plus* metronidazole	Third- or fourth-generation cephalosporin (ceftazidime or cefepime) *plus* metronidazole Ceftazidime/avibactam *plus* metronidazole[g] Ceftolozane/tazobactam *plus* metronidazole
Fluoroquinolone based[e]	Ciprofloxacin or levofloxacin, each in combination with metronidazole[g]	Ciprofloxacin in combination with metronidazole[h]
Monobactam based		Aztreonam *plus* vancomycin[f] *or* clindamycin *plus* metronidazole

[a]Empirical antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated in culture.
[b]Applies mainly to low-risk patients with community-acquired intraabdominal infections.
[c]Applies to health care–associated and tertiary peritonitis cases, and some high-risk and severe community-acquired intraabdominal infections. **However, tigecycline should NOT be used as empirical therapy for health care–associated or tertiary infection owing to inactivity of tigecycline against *Pseudomonas aeruginosa.***
[d]In vitro activity may be less, compared to alternative antibiotics; 4.5 g dose recommended.
[e]Fluoroquinolone-resistant *Escherichia coli* has become common in some communities, and fluoroquinolones should not be used unless hospital surveys indicate at least 90% susceptibility of *E. coli* to fluoroquinolones.
[f]Risk of mortality may be greater compared with alternative antimicrobials.
[g]Clinical cure rates were lower than those achieved with meropenem in a phase III trial, with baseline creatinine clearance (CrCL) of 30 to 50 mL/min. However, patients treated with ceftazidime-avibactam received a 33% lower daily dose than is currently recommended for patients with this CrCL.
[h]Because *Bacteroides* strains are resistant to these fluoroquinolones, addition of metronidazole is necessary.

The designation "high risk" is also assigned to community-acquired infections in patients who are elderly, have significant medical comorbidities including immunocompromising conditions, diffuse peritonitis, or delay or inability in achieving adequate débridement or drainage.[2] Travel to global geographic areas with higher rates of resistant or known colonization with such organisms, and a history of extensive or recent antibiotic exposure are also factors that characterize a community-acquired peritoneal infection as high risk.[180,181] No one regimen has been consistently demonstrated to be superior or inferior. Table 74.6 lists antimicrobial agents and regimens that have been adequately studied in clinical trials for use in the treatment of intraabdominal

TABLE 74.6 Antibiotic Dosage for Peritonitis During Peritoneal Dialysis

DRUG	INTERMITTENT (PER EXCHANGE, ONCE DAILY)[a]	CONTINUOUS (ALL EXCHANGES)[b]
Aminoglycosides		
Gentamicin	0.6 mg/kg	LD: 8 mg/L MD: 4 mg/L
Tobramycin	0.6 mg/kg	LD: 8 mg/L
Amikacin	2.0 mg/kg	MD: 4 mg/L
Cephalosporins		
Cefazolin	15 mg/kg	LD: 500 mg/L MD: 125 mg/L
Cefepime	1 g	LD: 500 mg/L MD: 125 mg/L
Ceftazidime	1–1.5 g	LD: 500 mg/L MD: 125 mg/L
Cefotaxime	1 g	LD: 500 mg/L MD: 125 mg/L
Penicillins		
Ampicillin	ND	MD: 125 mg/L
Oxacillin	ND	MD: 125 mg/L
Penicillin G	ND	LD: 50,000 U MD: 25,000 U
Piperacillin	ND	LD: 500 mg/L MD: 250 mg/L
Quinolones		
Ciprofloxacin	ND	LD: 50 mg/L MD: 25 mg/L
Others		
Vancomycin	15–30 mg/kg every 5–7 days[c]	LD: 1000 mg/L MD: 25 mg/L[d]
Aztreonam	ND	LD: 1000 mg/L MD: 250 mg/L
Daptomycin	ND	LD: 100 mg/L MD: 20 mg/L
Linezolid	200–300 mg/day PO	MD: 200–300 mg/day PO
Trimethoprim-sulfamethoxazole	160 mg TMP/800 mg SMX (double strength) 2 × day PO	MD: 160 mg TMP/800 mg SMX (double-strength tablet) 2 × day PO
Combinations		
Ampicillin-sulbactam	2 g every 12 h	LD: 1000 mg/L MD: 100 mg/L
Imipenem-cilastatin	1 g every 12 h	LD: 500 mg/L MD: 200 mg/L
Antifungals[e]		
Amphotericin B	NA	1.5 mg/L
Fluconazole	200 mg every 24–48 h	200 mg/L IP or PO daily

[a]Dwell time for dialysate exchange with antibiotic(s) must be ≥6 hours.
[b]Increase dose by 25% if patient urine output >100 mL/day.
[c]Based on serum drug levels.
[d]Adjust dose based on serum drug levels.
[e]Systemic administration preferred. Fluconazole, 200 mg/day IV or PO; amphotericin B, 0.6 mg/kg per day IV; caspofungin, 70 mg day 1, then 50 mg/day IV; micafungin, 100 mg/day IV; anidulafungin, 200 mg day 1, then 100 mg/day IV; voriconazole, 400 mg twice daily day 1, then 200 mg/day PO.
IP, Intraperitoneal; *LD,* loading dose; *MD,* maintenance dose; *NA,* not applicable; *ND,* no data; *PO,* orally; *SMX,* sulfamethoxazole; *TMP,* trimethoprim.
Modified from Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. *2016;36(50);481–508; Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America.* Clin Infect Dis. *2016;62(4):E1–E50.*

infections. However, most intraabdominal infection antibiotic trials were conducted before the emergence of multidrug-resistant organisms, which are now more frequently encountered as significant pathogens in these infections.[182] Along with this, the determination of antimicrobial susceptibility of bacteria based on interpretive susceptibility breakpoint criteria established by the Clinical Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has been modified in recent years.[93,183] Such alterations may serve to lessen the reliability of previously studied and recommended antibiotics used to treat intraabdominal infections because agents that were once believed to be adequate may now be less dependable, taking into account established pharmacodynamic principles.[184] In general, antibiotics from the carbapenem class have been the most active agents against pathogens involved in intraabdominal infections. Nevertheless, in certain geographic areas the spread of carbapenem-resistant genes, resulting in the emergence of various carbapenem-resistant phenotypes (*K. pneumoniae* carbapenemase [KPC], IMP, Verona integron-encoded [VIM], and New Delhi metallo-β-lactamase [NDM]), has increased and potentially could threaten the available options for treating multidrug-resistant organisms.[185]

Antimicrobial therapy should be started immediately after appropriate specimens (blood and, if possible, peritoneal fluid) are obtained for culture. Antimicrobial therapy is often started before the completion of in vitro antimicrobial sensitivity testing of the specific facultative pathogens. In addition, rapid isolation, identification, and in vitro sensitivity testing of anaerobes, in contrast to testing of facultative bacteria, are not possible in many community hospitals. Several factors account for the delay in obtaining anaerobic bacteriologic results. Infections caused by anaerobes frequently involve mixtures of five or more microorganisms, and cultures require long periods for growth and isolation. In addition, in vitro sensitivity testing by the conventional disk diffusion technique has not been standardized for anaerobes.[130] The results of these tests are influenced to a large extent by the growth rate of the bacteria, inoculum size, pH and type of medium, duration of incubation, and carbon dioxide concentration in the atmosphere. In vitro studies of the stability of the β-lactam antibiotics when exposed to reducing agents such as mercaptoamines (cysteine), which frequently are incorporated in media used for the growth of anaerobes, have revealed that these compounds are able to open the β-lactam ring and to inactivate penicillins. Susceptibility of anaerobic organisms can be determined reliably, however, with the broth or agar dilution technique with the use of appropriate media. Because these tests are generally performed by research laboratories, knowledge about the antimicrobial susceptibility of anaerobes is obtained from periodically published reports on anaerobic isolates by centers that specialize in performing these tests. Initial chemotherapy is usually empirical, based on the most reliable and least toxic antimicrobial agents for the most probable anaerobic and facultative pathogens. Reports on in vitro sensitivity (usually reliable only for the facultative or aerobic organisms) enable physicians to subsequently adjust the initial regimen to more specific therapy.

Because these infections are commonly polymicrobial, a broad spectrum of antimicrobial activity is required. Data suggest that survival in patients with sepsis, including that due to intraabdominal infection, is diminished if initial therapy is inadequate, regardless of the adequacy of subsequent treatment.[158,186] The ideal regimen remains controversial. The animal model of intraabdominal sepsis showed the necessity of treating the facultative enteric gram-negative bacillus *(E. coli)* and the anaerobic gram-negative bacillus *(B. fragilis).* Empirical efficacy of an antimicrobial regimen active against *E. coli* and *B. fragilis* has been well established. The need for intraoperative cultures to document the etiologic microorganisms and their antimicrobial susceptibilities has been controversial because postoperative changes based on results of intraoperative cultures may not improve outcome.[187]

Drugs active against anaerobic bacteria may be inactive against the accompanying aerobic or facultative pathogens in the mixed infections and vice versa. For this reason, combinations of usually two or three drugs are used. These combinations of antimicrobial agents are selected for their activity against most of the more virulent pathogens in the infective mixture (e.g., the Enterobacteriaceae and *B. fragilis*), although monotherapy for polymicrobial intraabdominal infection is now possible

because of the availability of broad-spectrum agents with activity against aerobes and anaerobes.

Antibiotics need not be active against every pathogen isolated. It is apparent that if only some of the organisms can be eliminated, the synergistic effect may be removed and the patient's defenses may be able to eradicate the remaining organisms. Although not recommended, clindamycin alone (which has no activity against Enterobacteriaceae or enterococci) has been reported to be sufficient treatment for some patients with infections resulting from a mixture of Enterobacteriaceae, enterococci, and anaerobes.[188]

Although enterococci are found in about 20% of intraabdominal infections, the exact role they play in polymicrobial intraabdominal infection and the need for an antimicrobial regimen specific for these organisms are controversial.[189–191] In several studies, patients were treated successfully with clindamycin and gentamicin despite absence of activity of this therapeutic regimen against enterococci.[192,193] Selective therapy against *E. coli* and *B. fragilis* that has no or borderline in vitro antimicrobial activity against enterococci has been found to be sufficient to reduce enterococcal counts.[194] Nevertheless, in animal models of experimental polymicrobial intraabdominal infection, enterococci have been found to be a significant component of the inoculum; as such, they enhance abscess formation, weight loss, bacteremia with *B. fragilis* and *E. coli,* and mortality.[194] Similarly, clinical reports have emphasized the importance of enterococci in intraabdominal infection[195] and noted the emergence of enterococcal abscesses and bacteremia supervening after treatment of intraabdominal sepsis with antimicrobial agents that lack significant in vitro antienterococcal activity.[196–199] Enterococci have emerged as major nosocomial pathogens, undoubtedly as a result of their inherent resistance to many commonly used antimicrobial agents and their acquisition of resistance to previous standard therapy (i.e., ampicillin, aminoglycosides, and the glycopeptides vancomycin and teicoplanin).[200–202] Only clinically unproven older antimicrobial agents (e.g., doxycycline, colistin, chloramphenicol) and a few newer antimicrobial agents (e.g., a combination of two streptogramin antibiotics [quinupristin-dalfopristin], linezolid, daptomycin, tigecycline) are available as potential therapy for infections caused by these multidrug-resistant and vancomycin-resistant strains of enterococci.

The efficacy of agents with antienterococcal activity in preventing emergence of enterococcal superinfection is unknown. A multicenter study of intraabdominal infection[203] demonstrated that the presence of enterococci in the initial culture, independently from the APACHE II score, was predictive of the failure of broad-spectrum antimicrobial regimens that lacked specific enterococcal activity. APACHE II score, age, length of preinfection hospital stay, and postoperative infections were predictive of the presence of enterococci. It is unclear whether inclusion of antienterococcal therapy would improve outcome in these high-risk patients, although one study suggested that postoperative addition of antienterococcal antimicrobial therapy after results of intraoperative peritoneal cultures were known did not lower the mortality rate, whereas other studies have suggested that this practice may prove beneficial.[204–206] At present, the available evidence suggests that routine coverage against enterococci is not necessary for patients with community-acquired intraabdominal infections but should be given to patients with prior cephalosporin or fluoroquinolone use (which may select for enterococci), immunocompromised patients, patients with prosthetic heart valves or vascular heart disease, those with hospital-acquired intraabdominal infection including postoperative peritonitis and tertiary peritonitis, and those with health care–associated infections from whom enterococci are recovered.[1,207] In these instances, empirical therapy should be directed against the probable species and strains that may be present with the knowledge that *Enterococcus faecium* has increasingly developed resistance to β-lactam antimicrobial agents and thus requires a glycopeptide drug for adequate activity.[208] Vancomycin-resistant enterococci (especially *E. faecium*) should be considered, particularly if the patient is at very high risk for an infection due to this organism, such as those who have had a previous surgical procedure, prolonged length of hospital stay, or extensive exposure to antibiotics, or individuals known to be colonized with vancomycin-resistant enterococci. Solid-organ transplant patients, especially recipients of liver transplants, with an intraabdominal infection originating in the hepatobiliary tree have a greater risk of vancomycin-resistant infections and colonization.[1,209]

In immunocompetent patients with low-risk community-acquired intraabdominal infections, *S. aureus* is rare, but it has been found to be more prevalent in health care–acquired infections, and many isolated strains exhibit methicillin-resistance. Its presence may be based on preinfection colonization or acquisition in the hospital or in patients with prolonged, complicated disease such as tertiary peritonitis.[7,190] Empirical therapy including agents with anti–methicillin-resistant *S. aureus* activity should be provided to patients with health care–associated intraabdominal infection who are known to be colonized or are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure.[1,6]

Candida spp. are cultured from about 20% of patients with acute perforations of the gastrointestinal tract.[1] The majority of candida peritonitis occurs in the health-care setting. The highest incidence is observed in patients who have more than one perforation, disruption in the upper gastrointestinal tract, surgically treated pancreatitis, or previous treatment with antibiotics.[210,211] Although *Candida albicans* remains the predominant species, *Candida glabrata* and other species have become more common.[212–214] Nonetheless, management of *Candida* spp. in polymicrobial infections is also controversial.[215,216] Published risk factors for invasive candidiasis in hospitalized patients, including the demonstration of *Candida* colonization at multiple other body sites,[217] have not been specifically proven to contribute to *Candida* peritoneal infections.[218,219] Although the isolation of *Candida* spp. from peritoneal fluid in cases of intraabdominal infection has been associated with increased mortality,[220] other than candidemia and other sites of invasive infection, the issue of attributable mortality remains unresolved.[213,214] Isolation of this microorganism from blood cultures—as the sole organism within residual or recurrent intraabdominal infection or as the predominant organism on Gram staining of peritoneal exudate—represents an indication for specific antifungal therapy plus drainage of abscesses, if present. Most authorities agree that even when *Candida* organisms are isolated in intraabdominal infections, antifungal agents are unnecessary unless the patient has recently received immunosuppressive therapy for malignancy, transplantation, or inflammatory disease or has postoperative or recurrent intraabdominal infection.[1] However, many experts recommend antifungal therapy if *Candida* is grown from intraabdominal specimens in patients with severe community-acquired and hospital-acquired intraabdominal infections.[207] Although no comparative trials in *Candida* peritonitis exist, an echinocandin (caspofungin, micafungin, anidulafungin) is the first antifungal agent of choice. Although fluconazole was previously recommended as initial therapy for invasive candidiasis, including peritonitis, accumulating data have suggested that the use of echinocandins results in improved outcomes.[221,222] However, fluconazole, 800-mg loading dose, then 400 mg daily, still remains an acceptable alternative for nonneutropenic patients who have had no recent azole exposure and are not colonized with azole-resistant *Candida* species.[223,224] Toxicities associated with amphotericin B have limited the role of this polyene antifungal in treating intraabdominal fungal infections.[223] Voriconazole may also be an appropriate alternative (also see Chapter 39).

The rise in bacterial resistance among aerobic gram-negative bacilli involved in health care–associated and, to an increasingly greater extent, community-acquired intraabdominal infections adversely affects outcomes. Antimicrobial resistance directly prolongs length of hospital stay, contributes to escalated overall costs, and increases morbidity and mortality, thus posing new challenges for selecting an adequate antimicrobial regimen for intraabdominal infections, particularly in those characterized as complicated and severe. The burgeoning resistance of aerobic gram-negative bacilli against generally used antimicrobial agents is heavily driven by the increased prevalence of ESBL production in Enterobacteriaceae isolates commonly involved in these infections.[225] The 2011 Study for Monitoring Antimicrobial Resistance Trends (SMART) found that 12.7% and 9.7% of *K. pneumoniae* and *E. coli,* respectively, produced ESBLs.[226] Although the signature phenotypic property of ESBL enzymes is the hydrolysis of extended-spectrum cephalosporins, the overexpression of other β-lactamases such as AmpC (the genetics of which typically are chromosomal but are capable of transfer to other bacteria via plasmids) further limits effective treatment of complicated

intraabdominal infections. Antibiotic resistance mediated by this enzyme is not overcome by the addition of β-lactamase inhibitors (e.g., clavulanate or tazobactam). In addition, resistance mechanisms such as altered drug targets, decreased outer membrane porin expression, and efflux pump regulation frequently coexist in β-lactamase–producing isolates, leading to multidrug-resistant, and at times extremely drug-resistant, pathogens. The use of older polymyxin and aminoglycoside antibiotics as well as newer combination β-lactam agents may need to be relied on when circumstances such as known colonization or involvement with such organisms exists.

The activities of various antimicrobial agents against the usual peritoneal pathogens and the results of clinical trials are discussed in the following sections.

Chloramphenicol. At a concentration of 16 μg/mL, chloramphenicol has activity against more than 99% of the anaerobic pathogens involved in intraabdominal infections, especially *B. fragilis.* The availability of equally effective and potentially less toxic antimicrobial agents to treat anaerobic infections (e.g., metronidazole, β-lactam/β-lactamase inhibitors, carbapenems) has all but eliminated the need for chloramphenicol.

Clindamycin. Clindamycin had been reported previously to inhibit more than 95% of the anaerobes, including *B. fragilis,* at a concentration of 8 μg/mL, and early clinical trials established the efficacy of clindamycin plus aminoglycoside. About 15% of the strains of *Clostridium* spp. other than *C. perfringens, Peptococcus* spp., and rare strains of *Fusobacterium* spp. have been reported to be resistant to clindamycin. Plasmid-mediated, transferable clindamycin resistance in anaerobic bacteria has been shown in vitro,[227] and clindamycin resistance among *B. fragilis* has become increasingly recognized in most medical centers.[228] Clindamycin is active against certain facultative gram-positive cocci, such as *S. aureus* and *Streptococcus pyogenes,* but not against enterococci, and it has virtually no activity against Enterobacteriaceae.

Diarrhea is reported to be the most common side effect of clindamycin therapy,[229] occurring at an incidence of 2% to 20%. The severity of the diarrhea varies, but it may be associated with pseudomembranous colitis in half of patients with diarrhea, as reported in one study.[230] Toxic megacolon, colonic perforation, and death have been reported rarely and were attributed to exotoxins produced by clindamycin-resistant strains of *Clostridioides difficile* (formerly *Clostridium difficile*). For these reasons and because agents with more reliable in vitro antianaerobic activity are available, clindamycin is no longer recommended for use in combination with other antimicrobial agents in the treatment of intraabdominal infections, except in patients in whom other agent options are either contraindicated or intolerable.

Metronidazole. Metronidazole is active against strict anaerobes; inhibits most *B. fragilis* strains, *Fusobacterium* spp., and *Clostridium* spp.; and has a unique bactericidal action against *B. fragilis* and *C. perfringens.* Resistance among *B. fragilis* to metronidazole is rare, although it was detected among 12.3% of *B. fragilis* isolates in one South African survey.[231] The in vitro activity of metronidazole is poor, however, against aerobes, microaerophiles, and anaerobes that may become aerotolerant on subculture (i.e., certain anaerobic gram-positive cocci and sporeless gram-positive rods), although there is some in vivo evidence in animal models and humans that metronidazole has activity against *E. coli* and other aerobes in mixed aerobic-anaerobic infections.[232] The mechanism for this is poorly understood but may be related to the conversion by *B. fragilis* of metronidazole into metabolites with activity against *E. coli* and other aerobes. Nonetheless, because facultative gram-negative bacilli and microaerophilic gram-positive cocci (which are frequent copathogens in polymicrobial anaerobic infection) are resistant to metronidazole, the drug should be used in combination with another agent that is active against these pathogens to compensate for these defects in its spectrum.

In a retrospective study, the relative incidence of *C. difficile*–associated diarrhea and colonization was found to be lower after use of metronidazole than after clindamycin.[233] Metronidazole is one of the drugs of choice for treatment of this disease.

Tetracyclines. The large number of resistant anaerobes, especially *B. fragilis,* precludes the use of tetracycline. These antibiotics currently have limited if any utility in the treatment of intraabdominal infections.

Cephalosporins. *B. fragilis* and other *Bacteroides* spp. are usually resistant to the first-generation cephalosporins (e.g., cefazolin) and to some second-generation cephalosporins (e.g., cefuroxime). Cefoxitin is distinctly more active than any of the other second-generation cephalosporins against *Bacteroides* spp., but cefoxitin resistance has become a problem at many medical centers.[227,234] Cefotetan has activity similar to that of cefoxitin except that it is less active against the *B. fragilis* group (not including *B. fragilis*). These first- and second-generation cephalosporins are also active against most strains of *E. coli, Proteus mirabilis,* and *K. pneumoniae.* However, cefoxitin and cefotetan cannot be recommended for use in treating intraabdominal infections[1] because *B. fragilis* has become increasingly too resistant to these agents. The third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) and fourth-generation cefepime have shown significantly better activity against the Enterobacteriaceae. Only ceftazidime and cefepime have activity against *P. aeruginosa.* With a few exceptions, the third- and fourth-generation cephalosporins have relatively poor activity against *B. fragilis* and other *Bacteroides* spp., and the addition of metronidazole is required in order to ensure antianaerobic activity.

Regimens in which a third-generation cephalosporin is substituted for the aminoglycoside compare favorably with clindamycin plus aminoglycoside. Under selective pressure of antimicrobial therapy with third-generation cephalosporins, however, resistance emerges readily among certain gram-negative bacilli that produce chromosomal-encoded inducible β-lactamases, such as *Enterobacter, Serratia, Citrobacter, Morganella*, and *Acinetobacter* spp. and *P. aeruginosa.* These organisms have a high spontaneous mutation rate for constitutive production of large amounts of these β-lactamases, which confer resistance to all β-lactams except imipenem, meropenem, ertapenem, doripenem, and possibly cefepime (depending on the interpretive susceptibility breakpoint applied, CLSI vs. EUCAST[93]) and are poorly antagonized by the clinically available β-lactamase inhibitors, sulbactam, clavulanic acid, and tazobactam. Patients who are likely to be infected with these organisms (patients with prolonged hospital stays, prior antibiotic treatment, postoperative peritonitis, or tertiary peritonitis) are treated best with imipenem, meropenem, ertapenem, doripenem, a fluoroquinolone, tigecycline, or an aminoglycoside. Some authorities recommend against using cefepime as first-line therapy for ESBL-producing organisms, particularly because of the effect of greater concentrations of bacterial organisms, which raise minimal inhibitory concentrations (MICs) against such organisms.[235]

Strains of *K. pneumoniae* and to a lesser extent *E. coli* have acquired plasmid-encoded, ESBLs that inactivate all third-generation cephalosporins, especially ceftazidime, extended-spectrum penicillins, and aztreonam. These strains are also frequently resistant to the fluoroquinolones. These β-lactamases may be inactivated to some extent by sulbactam, clavulanic acid, and tazobactam, which confer activity to the β-lactam/β-lactamase inhibitor combinations containing these agents. The cephamycin antibiotic agents cefoxitin and cefotetan demonstrate in vitro activity against several ESBL-producing Enterobacteriaceae but lack clinical trial data assessing their effectiveness in infections with these pathogens. ESBL rates for the two most common aerobic gram-negative bacilli, *E. coli* and *Klebsiella* spp., isolated from intraabdominal infections were found to have increased from 1.7% and 3.2% in 2005 to 7.3% and 13.1% in 2012, respectively, in North America,[98] with even greater increases occurring in various other parts of the world.[93] Imipenem, meropenem, ertapenem, doripenem, and to a lesser degree cefepime (see earlier), along with tigecycline, are most active against these strains. Two new cephalosporin/β-lactamase inhibitor combinations with improved activity against resistant gram-negative bacilli have been approved for the treatment of intraabdominal infections. Ceftolozane is a fifth-generation cephalosporin administrated with tazobactam. This oxyimino-aminothiazolyl cephalosporin's unique chemical structure improves its antimicrobial activity against AmpC β-lactamase–producing Enterobacteriaceae, and the β-lactamase inhibitor tazobactam component affords activity against class A and C β-lactamases. However, this combination antibiotic remains susceptible to degradation by *K. pneumoniae* carbapenemase (KPC) and metallo-β-lactamase (MBL)–producing strains of bacteria. Currently, its greater affinity for attachment to penicillin-binding proteins and ability to evade efflux pumps provides ceftolozane-tazobactam the distinction of being the most potent agent against *P. aeruginosa,* including many strains with documented resistance to ceftazidime and carbapenems. Similarly, ceftazidime in combination

with the novel non–β-lactam/β-lactamase inhibitor avibactam has proven active against most strains of Enterobacteriaceae including ESBL- and AmpC β-lactamase–producing isolates, with the added feature of considerable in vitro activity against KPC-producing Enterobacteriaceae but not MBL producers. Owing to their insufficient activity against anaerobic bacteria, both of these agents require the addition of metronidazole in treating intraabdominal infections and have been proved to be noninferior compared with meropenem in complicated intraabdominal infection phase III clinical treatment trials.[236–238] However, for reasons not entirely clear, both of these combination antibiotics were found to be less effective than meropenem in subgroups of patients with renal insufficiency.[239]

Penicillins. Penicillin G and ampicillin have excellent activity against anaerobes, with the exception of β-lactamase–producing anaerobic gram-negative bacilli, such as *Bacteroides* spp. (especially *B. fragilis*) and *Prevotella* spp. Ampicillin had been active against 70% to 80% of the strains of *E. coli,* although the percentage of resistant strains has been significantly increasing. Almost all strains of *P. mirabilis* are still inhibited by ampicillin. There is some evidence that penicillin G may fail to achieve inhibitory concentrations at sites of *B. fragilis* infection because of a reduction in penetration of penicillin into infected sites and inactivation of the drug by *B. fragilis.* Therapeutic failures despite high doses of penicillin for *B. fragilis* bacteremia have been well documented. These drugs currently have limited use, if any, in the treatment of intraabdominal infections.

About 80% to 90% of strains of *B. fragilis* may be sensitive to high concentrations (MIC ≤125 μg/mL) of the available extended-spectrum penicillins piperacillin and ticarcillin,[240,241] and the clinical experience with these drugs in polymicrobial anaerobic infections has been favorable.[242] The spectrum of these penicillins also includes most aerobic enteric gram-negative bacilli and *P. aeruginosa* but is not likely to include *K. pneumoniae* and many strains of *E. coli* as a consequence of β-lactamase production. In addition, ticarcillin is inherently much less active than piperacillin against enterococci and *P. aeruginosa.* The combination of ticarcillin or piperacillin with the β-lactamase inhibitors clavulanic acid or tazobactam confers activity against a large proportion of β-lactamase–producing strains of anaerobic gram-negative bacilli, *E. coli,* and *K. pneumoniae* (greater for piperacillin-tazobactam)[243–245] but does not confer significant activity against the chromosome-encoded, inducible, β-lactamase–producing strains of *Serratia* spp., *Enterobacter* spp., *P. aeruginosa, Citrobacter* spp., *Acinetobacter* spp., and *Morganella* spp. Newer ESBL-producing strains of these aerobic bacilli will not be inhibited by these extended-spectrum penicillins, and there are few proven clinical efficacy data for these combination agents against such ESBL producers in the treatment of high-inoculum infections that may overcome the action supplied by the β-lactamase inhibitor. With the CLSI's lowering of MIC breakpoints that are currently used in most microbiology laboratories for cephalosporins and monobactams,[246] specific additional tests to confirm the presence of β-lactamase are now not necessarily reported. However, because such breakpoints for β-lactam/β-lactamase inhibitor combination antibiotics, in particular piperacillin-tazobactam, remain high (i.e., susceptible <16/4 mg/L, resistant >128/4 mg/L), this agent is commonly chosen with confidence to treat higher-risk patients or those with more severe intraabdominal infections, discounting the concern that the pharmacodynamic action needed to optimize bacterial killing may not be achievable for these higher-MIC isolates.[247] Combining the β-lactamase inhibitor sulbactam with ampicillin restores activity against many community-acquired β-lactamase–producing bacteria that had developed resistance to ampicillin, including *E. coli, Klebsiella* spp., and *Bacteroides* spp.[243] This combination agent is inactive against nosocomial pathogens, such as *Enterobacter* spp., *Serratia* spp., and *P. aeruginosa.* Monotherapy for polymicrobial anaerobic intraabdominal infection is possible with β-lactam/β-lactamase combinations, such as ticarcillin-clavulanate (no longer available in the United States) and piperacillin-tazobactam, because of their broad spectrum of activity against aerobes and anaerobes. However, because of the significant rise in global resistance rates to Enterobacteriaceae, including 34% and 45% of health care– and community-acquired strains of *E. coli,* respectively, found to be nonsusceptible to ampicillin-sulbactam,[94] this combination agent can no longer be recommended for treatment of intraabdominal infections.[1,6]

Carbapenems and aztreonam. The carbapenem antibiotics imipenem, meropenem, ertapenem, and doripenem have a broad antimicrobial spectrum,[248] with activity against almost all aerobic and anaerobic pathogens, although *E. faecium* are resistant. Meropenem is slightly more active than imipenem against gram-negative bacilli and slightly less active against gram-positive cocci. Doripenem combines the broad-spectrum coverage of imipenem and meropenem with more potent activity against *P. aeruginosa.* The activity of ertapenem is similar to that of the other carbapenems, but ertapenem is not active against enterococci and *P. aeruginosa,* thereby relegating its use to lower-risk patients with community-acquired infections.[249] Its once-daily dosing (facilitating outpatient intravenous therapy) and possible decreased induction of multidrug-resistant gram-negative bacilli[250] may make it appealing. Conversely, experts have expressed concern that broad use of ertapenem may hasten the appearance of carbapenem-resistant Enterobacteriaceae, *Pseudomonas,* and *Acinetobacter* species.[1,94] The carbapenems are resistant to most β-lactamases, including chromosome-encoded, inducible β-lactamases produced by bacteria, such as *Enterobacter* spp., *Serratia* spp., and *P. aeruginosa,* and the plasmid-encoded, ESBLs produced by *K. pneumoniae* and *E. coli.* The carbapenems are susceptible, however, to metallo-β-lactamases produced by rare strains of *B. fragilis* and *S. maltophilia.*[248] Monotherapy for polymicrobial anaerobic intraabdominal infection is possible with the carbapenems because of their broad spectrum of activity against aerobes and anaerobes.[251–253] Subsequently, taking into account their reliable activity against multidrug-resistant organisms, the carbapenems (except for ertapenem because it lacks activity against *P. aeruginosa*) may be the drugs of choice for treatment of complicated intraabdominal infections, especially those that are health care associated. Unfortunately, as a consequence of growing resistance issues, there has been an increased dependence on carbapenems when confronted with high-risk patients having more severe complicated intraabdominal infections, which has created selection pressure for carbapenem resistance. A growing number of Enterobacteriaceae have become resistant to the carbapenems as a result of hydrolyzing enzymes that belong to the KPC serine β-lactamase, and the VIM and NDM metallo-β-lactamases, and this development may lead to extensively drug-resistant bacteria, which will limit the ability to treat patients with complicated intraabdominal infections.[185,254] Although in North America carbapenem resistance among Enterobacteriaceae species is uncommon, and only minor fluctuations in susceptibility to ertapenem and imipenem have been reported,[93,255,256] the surveillance network database for US hospitals from 2000 to 2009 found that in complicated intraabdominal infections, approximately 15% of *P. aeruginosa* strains demonstrated multidrug resistance, and 2% of aerobic gram-negative bacilli were carbapenem-resistant Enterobacteriaceae, mostly KPC-producing strains.[257] The same may not be able to be said for many other parts of the world. On such occasions, tigecycline and older antibiotics such as colistin and fosfomycin may be the only available treatment options.

The carbapenem β-lactamase combination drug meropenem-vaborbactam is highly active against many strains of carbapenemase-resistant Enterobacteriaceae, including KPC-producing isolates, but does not expand coverage to carbapenem-resistant *A. baumannii, P. aeruginosa,* or *S. maltophilia*.[258] Approved for treatment of complicated urinary tract infections and intraabdominal infections, it may be a viable alternative for treating cases of intraabdominal infections suspected or proven to involve multidrug-resistant bacterial pathogens.

Aztreonam, a monobactam antibiotic, has a spectrum of activity limited to aerobic gram-negative bacilli including *P. aeruginosa,* but inadequate activity against ESBL-producing strains of *E. coli* and *K. pneumoniae*.[259] Thus, it would be necessary to add an antibiotic with activity against microaerophilic and aerobic gram-positive cocci, such as vancomycin or clindamycin.[260] Activity against anaerobes would also be needed. Although clindamycin provides some antianaerobic activity, as previously mentioned, the antianaerobic activity of clindamycin is no longer adequately dependable to recommend its routine use. Thus, an antianaerobic drug such as metronidazole would be necessary in addition to aztreonam along with either vancomycin or clindamycin. An aztreonam-based regimen is a useful option in those patients with known serious allergic reactions to other β-lactam antibiotics, because

cross-reactivity in β-lactam–hypersensitive individuals is not known to occur with this monobactam agent.[261]

Aminoglycosides. Aminoglycosides are active against many gram-negative aerobic bacilli and were once considered a major component of intraabdominal infection treatment regimens. Over the decades of aminoglycoside use, aminoglycoside resistance has increased, however, and other antibiotic classes with predictable activity against gram-negative aerobic bacilli have become available. Amikacin, which is less susceptible to some gentamicin-modifying and tobramycin-modifying enzymes, nevertheless may be active against gentamicin-resistant or tobramycin-resistant pathogens. In some medical facilities, many gram-negative bacilli are currently found to be resistant to aminoglycosides, however, and the MICs of sensitive pathogens have increased steadily close to breakpoint concentrations. For optimal pharmacodynamic effects of aminoglycoside antibiotics, serum levels should be at least 10 times the MIC of the pathogen. Persistent inhibition of growth of the pathogen after brief exposure to an aminoglycoside (the postantibiotic effect) allows the serum levels of aminoglycosides to decline to less than the MIC of the pathogen during the dosing interval without loss of efficacy. Because aminoglycoside nephrotoxicity and perhaps ototoxicity are dependent on time, not concentration, high peak serum levels to maximize efficacy can be achieved without excess toxicity if the dosing interval is lengthened. This is the rationale for giving the total daily aminoglycoside dose as a single dose every 24 hours in patients with normal renal function, rather than giving the daily dose in two (amikacin) or three (gentamicin or tobramycin) equally divided doses every 24 hours. Single daily dosing of the aminoglycoside may be necessary to achieve serum levels that are at least 10 times the MIC of sensitive pathogens that have MICs close to breakpoint concentrations. The serum concentrations of gentamicin are unpredictable after a dose based on the body weight, so peak and trough serum levels must be confirmed by any of the various assay methods available.[262] The numbers of severely ill patients with intraabdominal sepsis studied are too limited, however, to permit recommendation of the general use of single daily dosing of these drugs.

Aminoglycosides are inactive against obligate anaerobes, and their activity against sensitive pathogens is antagonized by an anaerobic environment and by reducing substances, such as sulfhydryl compounds. Aminoglycosides are also not active in acidic conditions. Anaerobic and acidic conditions are frequently present in intraabdominal abscesses. In contrast, the β-lactams are relatively nontoxic, can be used in concentrations that are many times higher than the MIC for the pathogen, and are active under anaerobic or acidic conditions. The β-lactams are probably more reliable antibiotics than the aminoglycosides against sensitive pathogens. In two meta-analyses of well-conducted trials, aminoglycoside-based regimens were deemed inferior compared with several other regimens for the treatment of patients with intraabdominal infections.[263,264] For efficacy reasons, and because of toxicity concerns, the use of aminoglycosides to treat intraabdominal infection has been questioned; aminoglycosides are no longer recommended for routine use.[1,265] If indicated on the basis of in vitro sensitivity testing, β-lactams should be used in preference to aminoglycosides. An aminoglycoside may be included with a β-lactam antibiotic in the initial antimicrobial regimen for patients who are critically ill or in whom a resistant pathogen (e.g., *P. aeruginosa*) is suspected, as in empirical treatment of complicated health care–associated infections. They may also be necessary in the severely β-lactam–allergic patient infected with a multidrug-resistant aerobic gram-negative bacilli when no alternative active antibiotic exists.

Fluoroquinolones. The fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, and moxifloxacin) are active against almost all aerobic gram-negative bacilli. Ciprofloxacin remains the most potent fluoroquinolone against *P. aeruginosa.* Levofloxacin and moxifloxacin are more active than the older fluoroquinolones against gram-positive cocci, although enterococci and methicillin-resistant *S. aureus* tend to be less susceptible than other gram-positive cocci. In contrast to other fluoroquinolones, moxifloxacin is active against obligate anaerobes.[266,267] Concerns about resistance of anaerobes to moxifloxacin have been raised, although no existing data demonstrate suboptimal clinical outcomes or lower anaerobic susceptibility to this fluoroquinolone.[6,268]

Because of their ability to kill bacteria in the exponential and the stationary phases of growth, the fluoroquinolones are valuable antimicrobial agents for the treatment of intraabdominal infections, including abscesses. However, fluoroquinolones should be used judiciously; especially because *E. coli* resistance has emerged internationally.[94,269] Fluoroquinolones have now been found to have plasmid-mediated resistance. In treating patients with community- or health care–acquired intraabdominal infections of high severity, fluoroquinolone antibiotics should not be used unless local and hospital microbiologic surveys indicate that more than 90% of *E. coli* strains remain susceptible to these agents.[1,6]

Currently, three fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) are available for parenteral administration. These fluoroquinolones are also well absorbed after oral administration and are concentrated in tissues such that tissue levels greatly exceed the MICs of many sensitive pathogens. With current fluoroquinolone dosing regimens, serum levels may be inadequate to treat susceptible pathogens with relatively high MICs (e.g., >0.5 μg/mL of ciprofloxacin), which include some strains of *P. aeruginosa,* enterococci, and *S. aureus,* especially the methicillin-resistant strains. If such organisms can be anticipated (e.g., in nosocomial infections), additional antimicrobial agents may be necessary to broaden the spectrum of an empirical regimen. The addition of an antimicrobial agent active against anaerobic bacteria and aerobic or microaerophilic gram-positive cocci (e.g., clindamycin, ampicillin-sulbactam, amoxicillin–clavulanate acid) would be required if the use of ciprofloxacin were considered for secondary intraabdominal infection. The use of levofloxacin, even combined with a second agent with reliable activity against anaerobic gram-negative bacilli for the treatment of intraabdominal infections, does not have any published support, and perhaps this fluoroquinolone should be reserved for respiratory and urinary tract infections for which it may be better suited.[270] Moxifloxacin is the only fluoroquinolone that has been studied and approved as a single agent for the treatment of complicated intraabdominal infections. It has been determined to be noninferior to β-lactam/β-lactamase inhibitors, cephalosporin-based regimens, and carbapenems in several comparator studies.[271–273] However, its use should be cautioned against in patients who have recently been treated with any fluoroquinolone antibiotic because these individuals may harbor moxifloxacin-resistant strains of *B. fragilis* and other fluoroquinolone-resistant microorganisms.[274] β-Fluoroquinolone–based intraabdominal infection regimens are practical treatment options in lower-risk patients who are severely allergic to β-lactam antibiotics in settings where the degree of *E. coli* fluoroquinolone resistance is not high.

Tigecycline. The first glycylcycline antibiotic approved for the treatment of complicated intraabdominal infections was tigecycline.[275] With an expanded spectrum of activity against aerobic and facultative gram-positive and gram-negative bacteria, in addition to anaerobic bacteria, this parenteral agent was found to be at least as efficacious as imipenem in a trial treating patients with complicated intraabdominal infections.[276] However, a pooled analysis of trials involving tigecycline, including one trial in complicated intraabdominal infection, demonstrated an increased risk of death among patients receiving tigecycline compared with patients receiving comparator antibiotics, which has since led to a black box warning from the US Food and Drug Administration (FDA) and a recommendation against the use of tigecycline in severe infection.[7,274] It nevertheless has a distinct mechanism of antibacterial action that is not affected by resistance encountered with β-lactam and fluoroquinolone agents and therefore may serve a need in treatment of patients with intraabdominal infections with multidrug-resistant gram-negative bacilli, including ESBL- or carbapenemase-producing organisms. In addition, tigecycline has reliable activity against vancomycin-resistant strains of enterococci and methicillin-resistant *S. aureus* and in vitro activity against *A. baumannii,* but not *P. aeruginosa.* One limitation with the use of tigecycline may be the relatively high incidence of nausea and vomiting experienced by patients treated with this agent.

Eravacycline. Eravacycline, an injectable synthetic fluorocycline antibiotic, belongs to the tetracycline group of antibiotics. Like tigecycline, eravacycline has a broad spectrum of antibacterial activity against a wide variety of multidrug resistant gram-negative, gram-positive, and anaerobic bacteria, including methicillin-resistant staphylococci,

vancomycin-resistant enterococci, extended-spectrum β-lactamase and some carbapenem-resistant Enterobacteriaceae, as well as resistant *A. baumanni*.[276a] Eravacycline demonstrates 2- to 8-fold more in vitro potency than tigecycline, but, similar to this agent, it also lacks reliable antipseudomonal activity. Based on the results of two pivotal phase 3 trials (IGNITE 1 and IGNITE 4) demonstrating noninferiority to ertapenem and meropenem, respectively, it has been approved for use as monotherapy for the treatment of complicated intraabdominal polymicrobial infections.[276b,276c] The most common adverse reactions observed in clinical trials were infusion site reactions, nausea, and vomiting. Dosing is weight-based given as an intravenous infusion at 1 mg/kg every 12 hours, with no required adjustment of dose required in patients with renal impairment.

Pharmacodynamic Considerations

A Cochrane Collaboration review of antimicrobial therapy for intraabdominal infections was unable to demonstrate clinical superiority of any one regimen.[277] Using Monte Carlo simulations to model the probability of adequate coverage of pathogens commonly isolated from patients with intraabdominal infections, the researchers revealed substantial variability among regimens.[92] Pharmacodynamic data modeled against MIC information for a variety of bacteria, obtained from a large database for each antimicrobial agent, were expressed as the cumulative fraction of response (CFR), which is defined as the expected population probability of target attainment for a specific drug and dose against a specific population of pathogens.[92] Target attainment, in turn, is based on the percentage of the dosing interval during which free drug concentration remains above the MIC (free T [time] > MIC), for agents whose killing is time dependent (e.g., β-lactams), or the ratio of the area under the concentration-time curve to the MIC for compounds whose killing activity is concentration dependent (e.g., fluoroquinolones). Whereas the carbapenems, piperacillin-tazobactam, ceftazidime, and cefepime all yielded CFRs exceeding 90%, ceftriaxone, ciprofloxacin, and levofloxacin each yielded a CFR of less than 82%. In cases in which exact clinical efficacy data are ambivalent, pharmacodynamic modeling may be a useful adjunct in choosing a treatment regimen.[92]

Duration of antimicrobial therapy. Antibiotic therapy should be given before, during, and after surgery to ensure adequate tissue and blood levels at which the antibiotic can combat local and metastatic spread of the infection. The duration of antimicrobial therapy after adequate surgery is usually 4 to 7 days and depends on severity of infection, clinical response, and normalization of the leukocyte count.[1,6] A recent study involving adults with community-acquired localized peritonitis observed that patients treated for 3 days had similar outcomes to those treated for 5 to 10 days.[278] In another study involving complicated intraabdominal infection, patients who had undergone an adequate source-control procedure had similar outcomes after being treated with a fixed-duration antibiotic course of approximately 4 days compared with those after a longer course of antibiotics of approximately 8 days.[279] Patients with secondary bacteremia from an abdominal source who received shorter courses of antibiotics, defined as 7 or fewer days, have been shown to have similar outcomes to those given traditional longer courses of antiinfective therapy.[280] Only a short course of antimicrobial therapy (24 hours) is required for sterile peritonitis that occurs in the peritoneal space around an infected intraabdominal organ that can be resected, such as the appendix in nonperforated appendicitis, or the gallbladder in acute cholecystitis.[281,282] Rates of infection in patients receiving perioperative antibiotics alone compared with longer courses of treatment in cases of nonperforated or ischemic gastrointestinal diseases have proven the same.[283] Similarly, contamination of the peritoneum with bacteria from a defect in the intestinal wall (e.g., immediately after penetrating abdominal trauma) also may necessitate only (1) operative intervention to remove the diseased organ and to stop continued peritoneal contamination and (2) a brief course of antimicrobial therapy, as would be indicated for surgical prophylaxis, limiting antibiotic administration to no more than 24 hours.[284,285] Persistent sepsis is suggestive of several complications: formation of an intraabdominal abscess, which necessitates drainage; continued contamination of the peritoneum from an inadequately controlled source; superimposed nosocomial infection with a resistant pathogen; or tertiary peritonitis.

The utility and proven benefit of antibiotic therapy to decrease secondary infection in noninfectious intraabdominal inflammatory disease has been an area of controversy. Quite often antibiotics are given to patients diagnosed with acute necrotizing pancreatitis who do not have a secondary infection complication. However, meta-analyses have failed to demonstrate any significant proven benefit, and the risks of bacterial resistance and complications, such as *C. difficile* infection, are increased when antibiotics are administered in this prophylactic fashion.[286–288] Studies looking at the need for antibiotics as part of the management of acute, uncomplicated sigmoid diverticulitis have found no difference in outcomes in those patients who were treated conservatively without antibiotics.[289,290] However, it may be prudent to apply this strategy only in lower-risk patients diagnosed with acute, uncomplicated left-sided diverticulitis. Similarly, a 5-year follow-up of antibiotic therapy alone for uncomplicated appendicitis had similar outcomes as in patients who underwent an appendectomy; the likelihood of late recurrence within 5 years was 39.1%.[291] (See Chapter 78.)

The antibiotic regimen should be adjusted to include the most efficacious, least toxic, and least expensive agents, when cultures have been finalized, with the proviso that therapy must have activity against anaerobes even when they are not isolated, because anaerobic bacteriologic techniques are frequently inadequate.

Patients able to tolerate oral intake may switch to oral therapy after an initial response to intravenous therapy.[1,203] Oral therapy allows earlier discharge for some patients and reduces costs and risks of infusion-related complications. When ileus no longer precludes oral intake, efficacy of oral therapy depends on the adequacy of absorption after oral administration of the antimicrobial agents, the availability of potent oral agents against the significant aerobic and anaerobic gram-negative bacilli and gram-positive cocci pathogens (i.e., *E. coli, B. fragilis,* and streptococcal species), and the effects of oral versus intravenous administration of these agents on bowel microbiota. The potential oral agents most studied for this purpose include amoxicillin-clavulanate, ciprofloxacin with metronidazole, and moxifloxacin, with recognition of the heightened prevalence of *E. coli* resistance to these agents. Levofloxacin is often substituted as the fluoroquinolone component but has never been studied for this purpose. Likewise, the oral cephalosporin drugs and trimethoprim-sulfamethoxazole have little proven evidence as antibiotics for the treatment of intraabdominal infections, but may be potential treatment options in specific cases. Although in many studies the orally administered antibiotics allowed treatment courses longer than the current recommendation of 4 to 7 days, the purpose of the switch should be the intention to shorten the length of parenteral antibiotic administration.[292,293]

The addition of antibiotics or antiseptics to intraperitoneal lavage fluid continues to be debated, and its efficacy intraoperatively or by continuous peritoneal lavage postoperatively remains unclear.[294,295] One study showed that irrigation of the peritoneal cavity with povidone-iodine decreased the frequency of intraabdominal abscess formation, in comparison with saline irrigation,[296] and other studies have suggested that including antibiotics in lavage fluid can reduce the incidence of postoperative infections. Povidone-iodine has been shown to be a potent inactivator of neutrophil functions such as chemotaxis and phagocytosis, however, and may have a detrimental effect.

Hyperbaric Oxygen

The increased oxygen tension attainable with hyperbaric oxygen therapy inhibits and kills *C. perfringens* and reduces the production of *C. perfringens* α-toxin. Hyperbaric oxygenation has been used clinically and experimentally for clostridial myonecrosis with some reported success. *C. perfringens* is a relatively oxygen-tolerant pathogen in comparison with other obligate anaerobes, and it is postulated that hyperbaric oxygen therapy may be at least as efficacious with anaerobic infections caused by these more oxygen-sensitive anaerobes. However, except for a few reports,[297] almost no clinical or experimental data are available. Hill[298] reported suppression of experimental liver abscesses caused by anaerobes in mice after treatment with hyperbaric oxygen therapy alone. In one study, it seemed that the use of hyperbaric oxygen therapy favorably affected the outcome of experimental sepsis in a rat model, perhaps by enhancing host defense mechanisms.[299] Consideration

also should be given to the hazards of hyperbaric oxygen therapy. See Chapter 50 for a more detailed discussion.

Gastrointestinal Drainage

In the presence of peritonitis, the patient should receive nothing by mouth. If no distention is present when treatment is instituted, continuous gastric suction is usually sufficient. For patients with distention when treatment is started and for patients who acquire distention despite gastric drainage, the small intestine should be intubated.

Water and Electrolyte Administration

The type of fluid replacement is determined in large part by the chemical abnormalities found. Early goal-directed volume resuscitation is essential in treating uncomplicated intraabdominal infections but becomes critical in cases of severe sepsis or septic shock. Regardless of whether the end point for resuscitation is mixed venous oxygen (>65%), correction of lactic acidosis, or normalization of base deficit, the goal of volume resuscitation is correction of cellular oxygen. In general, hypovolemia, dehydration, and metabolic acidosis predominate; therefore, plasma or albumin, Ringer's lactate solution, and 5% dextrose in water usually suffice. With regard to the types of fluids, timing, and amounts to be given, the recommendations put forth in the Surviving Sepsis Campaign should be followed.[186]

Blood and Plasma Transfusion

Although many patients recover from an illness satisfactorily with a hemoglobin of 8 or 10 g/dL, some surgeons recommend that the patient undergo transfusion to maintain levels of 12 to 13 g/dL in order to provide a margin of safety in the event of some complication, such as septic shock or upper gastrointestinal hemorrhage. A less liberal blood transfusion policy has been adopted by many medical centers.[300]

Respiratory Support

Fluid sequestered in the abdomen and loops of bowel distended by gas may elevate the diaphragm. Inflammation of the parietal peritoneum, including the diaphragmatic surface, leads to guarding and splinting of the muscular wall, which interferes with deep breathing and coughing. A subphrenic abscess may be responsible for splinting of the diaphragm. Retained bronchial secretions may lead to atelectasis and subsequent pneumonitis. These factors impair the ability to augment respiratory exchange in the presence of the increased expenditure of energy required by the inflammatory process, and this leads to hypoxemia and respiratory alkalosis. When the patient tires, the combination of metabolic and respiratory acidosis may develop and prove fatal.

Arterial blood gas studies are necessary to detect and quantitate respiratory decompensation. Measures aimed primarily at gastrointestinal decompression, elevation of the head of the bed, and control of the inflammation may improve respiration sufficiently. Administration of oxygen may improve arterial oxygen saturation. If these measures are inadequate, endotracheal intubation or tracheostomy should be performed without delay. A volume-cycled respirator should be used and adjusted to produce a partial pressure of oxygen of 80 to 100 mm Hg and a normal pH. If the partial pressure of carbon dioxide is then not normal, metabolic acidosis or alkalosis may be present and must be treated. As the intraabdominal process subsides, the patient may be able to breathe spontaneously again and may be weaned from the ventilator. In certain severe cases, positive end-expiratory pressure may also be necessary.

Operative Approach

Surgical intervention is aimed at controlling the source of peritoneal contamination and at débridement of necrotic tissue and foreign intraperitoneal matter.[301] Immediate surgical intervention within hours of presentation even in the medically unstable septic patient has been found to have a significant survival advantage.[302] In the majority of cases, intervention to control the source, and to restore normal gastrointestinal function and anatomy should be carried out within 24 hours; studies have indicated that postponement of source control beyond this time period has been associated with a greater risk of death.[303] Optimal management includes (1) bowel decompression (e.g., through proximal colostomy for perforation, diverticulitis, or colonic carcinoma); (2) closure of traumatic perforations and resection of a diseased, perforated viscus to stop continued peritoneal contamination with bacteria and adjuvants; and (3) drainage of any purulent collections, which reduces the bacterial inoculum, removes excessive levels of proinflammatory cytokines and adjuvants (e.g., fecal matter, food, blood, bile, barium) that would enhance the virulence of peritoneal infection, and eliminates anaerobic conditions. In the absence of perforation, when the disease process (e.g., acute appendicitis, necrotic bowel) is anticipated to advance, the involved organ is resected. Acute increase in intraabdominal pressure, which itself can lead to multiorgan dysfunction (e.g., acute pulmonary and renal failure, shock), necessitates decompression laparotomy; if necessary, the abdomen is left open and covered with a protective dressing.[92]

In complicated cases or severely ill patients, it may be necessary to perform an initial laparotomy for immediate source control with temporary abdominal closure followed later by a reexploration for definitive treatment.[304,305]

Operative intervention is generally not indicated for patients with primary peritonitis; in patients in whom the disease process subsides and localizes while the patient is being prepared for surgery; in moribund patients; or in patients with pelvic peritonitis caused by pelvic inflammatory disease, which usually responds to medical management. Stable, noncritical patients with localized intraabdominal infections including perforated appendicitis with localized phlegmon or periappendiceal abscesses; acute colonic diverticulitis with inflammation into the adjacent colonic tissues or small abscesses; and localized upper gastrointestinal perforations, may be treated conservatively with antibiotics alone, at times.[306–308] A similar treatment approach followed by a delay before surgery of days or even weeks may be warranted in other scenarios.[309,310]

Intraoperative peritoneal lavage with saline, after drainage of purulent peritoneal exudates, fecal matter, food, and other foreign debris, is standard procedure during laparotomy for peritonitis. Continuous postoperative peritoneal lavage for 48 to 72 hours or until the fluid is clear, with the use of large volumes of fluid to ensure dispersion of the fluid and to prevent loculations, has, however, not been effective.[294,295] Radical peritoneal débridement of all fibrinous deposits on peritoneal surfaces is, likewise, no longer thought to be effective.[311]

Initial reports were favorable for planned reexplorations in which laparotomies were performed at frequent intervals until the abdomen was macroscopically clean, regardless of the patient's condition, with additional surgical procedures (e.g., resections) performed as needed.[312] The abdominal fascia would be left open between laparotomies, with the abdominal wall defect bridged by saline-soaked gauze or by a temporary abdominal closure device such as mesh. On resolution of the septic process and establishment of granulation, the mesh would be removed and a skin graft would be applied to the granulating bed. These demanding and costly procedures have been complicated by multiple fistulas, wound contamination, incisional hernias, and secondary peritonitis with organisms such as enterococci or *Candida* spp.[313] Repeated entry into the inflamed peritoneum may escalate the cascade further. A review concluded that in the absence of randomized, controlled prospective trials with appropriate stratification of patients by severity of illness, evidence is now insufficient to determine whether these procedures improve outcome in severe diffuse peritonitis; nevertheless, they may be lifesaving in some patients.[313,314] In localized infection, local drainage alone is adequate because the risk of disseminating infection outweighs any possible benefit of removing foreign material that may have escaped mechanical removal.

Less invasive source-control procedures, including interventional radiologic percutaneous drainage of intraabdominal and pelvic fluid collections, are increasingly relied on when the infection is localized and a safe window for introduction of the drainage tube exists.[315] This treatment approach may also be the safest alternative in patients who could not tolerate a surgical procedure owing to their medical condition or who refused operation.

Use of multiple drains for drainage of the general peritoneal cavity is physically impossible because exudate and adhesions rapidly isolate and occlude the drains and may increase secondary infections. Drains are often placed, however, in a dependent point to which fluid can be

expected to gravitate or in an area of devitalized tissue that cannot be removed.

Prevention

To prevent postoperative peritonitis, the peritoneum must not be contaminated with gastrointestinal or vaginal secretions. In addition to use of good surgical technique, contamination can be avoided with early treatment of an intraabdominal infection. Leigh and coworkers[316] noted that the rate of wound infection in patients with perforated appendix was greater than 50% if no antimicrobial therapy was used but only 15% with appropriate therapy. Similarly, early use of antibiotics in penetrating wounds of the abdomen, especially wounds involving the colon, has been efficacious.[317] Surgeons also have used various means to reduce the complex gastrointestinal or vaginal flora before performing clean, contaminated surgery. Mechanical cleansing of the bowel with a low-residue diet followed by a liquid diet, cathartics, and enemas can reduce the total fecal mass and coliform count in the colon, although not the predominant anaerobic flora. The use of oral antibiotics preoperatively to reduce bowel flora is well accepted. *E. coli* in the colonic flora is sensitive to oral neomycin or kanamycin, whereas *B. fragilis* is frequently sensitive to erythromycin or metronidazole. Combinations such as neomycin and erythromycin base have been shown to be effective in reducing total bowel flora preoperatively and in decreasing the incidence of postoperative infection.[318]

Parenteral antibiotics have also been used in gastrointestinal and vaginal surgery prophylactically when there is a chance of contamination with normal microflora at the operative site (clean, contaminated surgery). Of these types of operations, 30% may be complicated by infections. The procedures involve cutting through the large bowel without significant spillage, compromising the blood supply of the large bowel, cutting through the stomach or small bowel when there is anticipated intraluminal bacterial overgrowth, appendectomy for appendicitis without rupture, repair of penetrating wounds of the abdomen, gallbladder surgery in an elderly patient, cesarean section after rupture of the membranes and labor, vaginal hysterectomy in a premenopausal woman, and radical pelvic surgery for gynecologic malignancy. Several studies have shown significant reduction in the frequency of postoperative infection, from as high as 30% to as low as 4% after prophylactic antibiotic use in clean, contaminated surgery.[284,319,320] The basic principle of antibiotic prophylaxis is to provide adequate tissue levels at the site of contamination and adequate blood levels during the procedure and for 24 hours after the procedure. See Chapter 313 for a more detailed discussion.

Peritonitis During Peritoneal Dialysis

Long-Term Peritoneal Dialysis

Peritoneal dialysis has been used successfully to treat uremia in patients with end-stage renal disease since the mid-1940s. Peritonitis was a frequently associated side effect that hindered the acceptance of chronic peritoneal dialysis until an improved access catheter was developed by Henry Tenckhoff in 1968. This catheter significantly decreased the incidence of peritonitis, but initial reports of patients undergoing CAPD with this catheter indicated peritonitis rates of more than six episodes per patient-year.[321] This rate has appeared to decline with the introduction of collapsible plastic bags, improved adapters (Y system), and better techniques.[322] However, peritonitis remains the major complication of CAPD today and is the chief reason for peritoneal catheter loss, discontinuation of peritoneal dialysis, and switch to hemodialysis.[323] Historically, it occurred at a rate of about one episode per patient-year (range, <0.5 to ≥3). Of patients, 45% experienced peritonitis at least once during their initial 6 months of CAPD treatment. This rate increased to 60% to 70% during the first year.[324,325] Centers now routinely report infection rates of less than one episode in 24 patient-months and as low as one episode in 60 patient-months.[326] Peritonitis recurs in 20% to 30% of patients. A small proportion of patients seem to have an unusually high frequency of peritonitis.

This disparity has been attributed partly to faulty sterile technique on the part of patients during self-administration of CAPD (touch contamination). The patient undergoing CAPD needs to perform a great number of sterile exchanges per year; a patient on continuous cycling peritoneal dialysis (CCPD), in comparison, performs fewer exchanges. With CCPD, the rate of peritonitis would be presumably lower because manipulation of the connections is required less frequently; this concept is supported by most but not all studies.[327,328]

Source of Infection and Risk Factors

The origin of infection in most cases seems to be contamination of the catheter by common skin organisms.[321] Alterations of skin flora in CAPD recipients[329] may lead to peritoneal contamination with enteric pathogens. A higher incidence of peritonitis seems to occur in patients undergoing dialysis who are carriers of nasal *S. aureus.* This carriage state increases the likelihood of developing exit site infections and tunnel infections in comparison with noncarriers, but the overall peritonitis rate of the two groups was not different in one study, although all cases of *S. aureus* peritonitis occurred in the carriers.[330] Pathogens may also contaminate the peritoneum from exit site infections and subcutaneous tunnel (periluminal) infections, transient bacteremia, and contamination of the dialysate delivery system during bag exchanges. As mentioned previously, enteric bacteria may also gain access to the peritoneal cavity by means of transmural migration through an intact intestinal wall after the introduction of hypertonic solutions into the peritoneum. This mechanism may account for enteric bacterial peritonitis in patients undergoing dialysis. On rare occasions, a vaginal leak may serve as a source of peritonitis. Endoscopic gastrointestinal (colonoscopy, sigmoidoscopy), gynecologic (hysteroscopy), and urologic (cystoscopy) procedures have been associated with a greater risk for the development of peritonitis in CAPD patients when a biopsy, polyp removal, or placement of an intrauterine device was performed.[322,331] The risk of peritonitis is also higher in CAPD patients who are chronically constipated, smoke, or have depression.[332,333] Polymicrobial infection with fecal organisms is suggestive of bowel perforation as a complication of catheter placement or secondary peritonitis from other causes.

Alterations in peritoneal defenses may increase the risk of peritonitis in patients undergoing CAPD. The antimicrobial function of peritoneal macrophages and PMN cells generally requires the presence of opsonins. A reduction in the levels of immunoglobulin G and C3 has been noted in peritoneal dialysis effluents in comparison with serum, and the concentrations of these crucial opsonizing agents are related inversely to the frequency of peritonitis.[334] Other important factors that impair host defense mechanisms are the low pH and high osmolality of peritoneal dialysis fluid, both of which can impair PMN leukocyte function and antibiotic efficacy. Newer peritoneal dialysis fluids containing glucose polymers (e.g., icodextrin) may be less detrimental to macrophage and PMN leukocyte activity. However, the use of more biocompatible dialysis fluids has not conclusively been found to decrease the risk of peritonitis.[335,336] The formation of biofilm on the catheter appears to contribute to relapsing or recurrent infection, and to decreased therapeutic responses and development of antimicrobial resistance.

Microbiology

Gram-positive organisms historically have constituted 60% to 80% of isolates, most commonly *S. epidermidis,* followed by *S. aureus, Streptococcus* spp., and diphtheroids. More recent surveys have found a decrease in single gram-positive organism cases and a concomitant increase in other, less previously involved pathogens. Staphylococcal isolates have been noted to grow on polymer surfaces and frequently produce an extracellular slime substance or biofilm (as just described) that may protect these bacteria from host defenses.[337] Vancomycin-resistant enterococci as nosocomial pathogens are now more frequently recognized in peritonitis cases and when encountered should raise concern for another possible intraabdominal process. Gram-negative organisms are obtained from 15% to 30% of isolates. *E. coli* is the most common, followed by *Klebsiella* and *Enterobacter* spp., *Proteus* spp., and *Pseudomonas* spp. Cases caused by gram-negative organisms have increased, according to a retrospective study of peritoneal dialysis-related peritonitis over a decade-long period.[338] Sources may include contaminated water, skin, urinary tract, bowel, and animal contacts (e.g., *Pasteurella multocida*). Less common pathogens include *Acinetobacter* spp., *C. albicans,* and anaerobic bacteria. Rare isolates include atypical mycobacteria (usually *Mycobacterium chelonae* or *Mycobacterium fortuitum*), *M. tuberculosis, Candida parapsilosis, Aspergillus fumigatus, Nocardia*

asteroides complex, and *Fusarium* spp. Although it is unclear whether peritoneal dialysis–related peritonitis can be caused by viruses, the risk of bacterial infection is believed to increase in patients with a viral infection.[339,340]

Polymicrobial peritonitis in patients undergoing peritoneal dialysis is usually assumed to be secondary to a primary intestinal process (e.g., bowel perforation) and usually necessitates surgical exploration.

Diagnosis

Diagnosis of peritonitis is made when microorganisms and an increased number of leukocytes are present in the dialysate in combination with a constellation of clinical findings that include abdominal pain and tenderness (60%–80% of patients), nausea and vomiting (30%–50%), fever (25%–50%), and diarrhea (10%).[321,341] Not all these criteria need to be met, however, for the diagnosis to be made.

The dialysate is almost always cloudy, and microscopic examination reveals a leukocyte count greater than 100 cells/mm^3 (in approximately 85% of cases, >500/mm^3), with neutrophils predominating. The length of the dwell time has an impact on the number of effluent cells. A low leukocyte count in dialysate may also be indicative of a tunnel infection and not peritonitis. Although a predominance of lymphocytes may be encountered with fungal and mycobacterial infections, the majority of cases still manifest a larger number of neutrophils in the peritoneal dialysis effluent. A preponderance of eosinophils in the peritoneal fluid is seen in a self-limited condition called *eosinophilic peritonitis* that often follows placement of the Tenckhoff catheter and may represent allergy to the tubing. Peritoneal eosinophilia may also be present in fungal and parasitic peritonitis, may be related to chemical and drug (i.e., vancomycin) effects, and may be associated with icodextrin. Gram staining of the fluid reveals organisms in 9% to 50% of cases.[321] Peripheral leukocytosis is a poor indicator for peritonitis in this group of patients. Blood cultures are rarely positive, in contrast to the 30% to 50% positive rate in other types of intraabdominal infections.

Peritonitis with negative cultures occurs in 5% to 10% of cases. Constant flow of dialysis fluid into and out of the peritoneal cavity dilutes the microbial density and may falsely lower the rate of positive results of dialysate culture. Negative cultures also may result from infection with fastidious organisms, from previous antimicrobial treatment, or from inadequate culture techniques (e.g., the collection of too little effluent). Culturing the sediment after centrifuging 50 mL of effluent dialysate or placing 5 to 10 mL of effluent dialysate in each of two blood culture bottles will enhance the recovery rate of organisms.[322] All cultures should be performed aerobically. Fungal, mycobacterial, and anaerobic cultures should be performed if clinically indicated (e.g., negative aerobic cultures). Causes of turbid dialysate, such as hemorrhage, fibrin or other proteins, chylous ascites, lymphoma and other malignancies, and prolonged dwell time, should be considered if the leukocyte count is below 300 to 500 cells/mm^3.[342,343]

Radiologic imaging studies are neither specific nor particularly helpful in the diagnosis of peritoneal dialysis–associated peritonitis. Small amounts of free intraperitoneal air can, at times, be discovered in asymptomatic patients.

Treatment and Prognosis

The prognosis of peritonitis in dialysis recipients is generally favorable. However, in one retrospective study, death occurred in 6% of 565 patients with a total of 693 episodes of peritonitis.[344] Mortality rates have also been found to vary according to the specific etiologic pathogen.[345] The duration of illness and positive peritoneal fluid cultures after institution of antimicrobial therapy is usually 1 to 4 days. Some infections, especially infections caused by *S. aureus, Pseudomonas* spp., or fungus, resolve more slowly, however, and may cause relapse more frequently.

Adequate levels of antimicrobial agents necessary to treat peritonitis successfully can be obtained in the peritoneal fluid through either the systemic or intraperitoneal route. Because CAPD-associated peritonitis is a localized infection, however, the intraperitoneal route is preferred and in fact has been found to be superior to the intravenous route.[346] The increased use of intraperitoneal antibiotic therapy for peritonitis has allowed most patients to be treated on an ambulatory basis. Hospitalization is indicated for patients who are severely ill or who are unable to manage the administration of intraperitoneal antibiotics at home. Although a variety of dosages and drugs can be found in the literature, the initial dosages recommended in Table 74.6 for intraperitoneal administration result in effective peritoneal fluid drug concentrations. Subsequent dosing is used to maintain these levels. The aim of the dosing regimen is to maintain a concentration of the drug in the peritoneal cavity fluid greater than the MIC of the offending pathogen for most, if not all, of the dosing interval. However, intermittent dosing regimens (antimicrobials given once daily) and continuous dosing regimens (given in each exchange) have been found to produce largely equivalent results.[346] With intermittent dosing, the antimicrobial must dwell for at least 6 hours. Physicians must exercise caution when reviewing the MIC and minimal bactericidal concentration data because these concentrations have been markedly increased when peritoneal dialysis effluent is used as the in vitro growth medium.[347]

Because of the lack of comparative, prospective clinical trials, no antimicrobial regimen is superior to another.[348] After cultures are obtained, initial antimicrobial therapy should be based on the results of Gram staining or, if the Gram stain is not helpful, directed against the most likely pathogens, providing coverage against both gram-positive and gram-negative organisms. A reasonable initial empirical regimen would be vancomycin in combination with an aminoglycoside. Vancomycin is preferable to a cephalosporin because of the frequency of β-lactam resistance (i.e., methicillin resistance) in staphylococci, which is also predictive of resistance to cephalosporins. The earlier finding of superior cure rates with glycopeptides compared with early generations of cephalosporins was unable to be confirmed in later trials.[346] Alternatively, ceftazidime, cefepime, or a carbapenem can be used in place of an aminoglycoside for empirical coverage of gram-negative organisms. Fluoroquinolones such as ciprofloxacin have also proven to be very effective agents against gram-negative pathogens, but owing to the increase in fluoroquinolone-resistant enteric bacteria, they should be avoided when known local fluoroquinolone resistance rates are greater than 10%.[349] Initial antibiotic choices should be modified, if necessary, after culture results are obtained. *P. aeruginosa* peritonitis is associated with high rates of treatment failure and relapses. Although the use of a combination of antipseudomonal agents pending susceptibility data is prudent practice, prolonged dual therapy has not been found to improve treatment outcomes. In addition to antibiotics, catheter removal is generally needed when *Pseudomonas* is the infecting pathogen. If vancomycin-resistant enterococci are determined to be the causative microorganism, linezolid or daptomycin should be administered.[350] The minimal length of therapy needed for dialysis-related peritonitis has not been determined, but the usual duration ranges from 10 days to 3 weeks. Longer antibiotic treatment courses (≥21 days) are required for peritonitis due to *S. aureus* and *P. aeruginosa.* Most patients with CAPD-associated peritonitis exhibit clinical improvement within 48 to 96 hours after initiation of antimicrobial therapy. If the signs and symptoms of peritonitis persist after 96 hours of therapy, reevaluation is warranted; the possibilities of resistant pathogens, unusual organisms (e.g., mycobacterial, fungal), and other intraabdominal processes should be considered.

In peritoneal dialysis patients who present with typical findings of peritonitis but have negative cultures, the same treatment regimens should be administered with durations of therapy similar to that for staphylococci.

Fungal peritonitis, usually caused by *C. albicans,* historically has been treated with amphotericin B,[351,352] although echinocandins are currently the preferred initial antifungal agent,[223] particularly in patients with prior exposure to azole antifungal agents. Patients should be transitioned to fluconazole when clinically stable and susceptibility to fluconazole has been confirmed. Initial therapy with fluconazole may be considered in selected patients, including those who are not critically ill.[223] If a mold is isolated, initial therapy with amphotericin B is warranted, although for *Aspergillus* spp., voriconazole given orally is a reasonable alternative. Some molds, including *Fusarium* spp., may be resistant to amphotericin, however. If CAPD is continued, amphotericin B should be given intraperitoneally, but it can cause appreciable abdominal pain when given by this route. There is also concern that amphotericin B–induced inflammation may cause adhesions that reduce the effective

TABLE 74.7 CAPD Peritonitis: Indications for Catheter Removal

Persistent infection at skin exit site or tunnel
Relapsing peritonitis with same organism—within 4 weeks
Refractory peritonitis—failure to respond within 5 days
Fungal, mycobacterial, *Pseudomonas aeruginosa* peritonitis
Intraperitoneal abscess
Catheter malfunction

CAPD, Continuous ambulatory peritoneal dialysis.

dialyzing surface. In most patients, CAPD-associated fungal infections fail to respond unless the catheter is removed; amphotericin B should be given intravenously for 10 days after catheter removal. Oral or intravenous fluconazole penetrates adequately into the peritoneal fluid to treat peritonitis due to susceptible fungi in CAPD recipients after the catheter has been removed. Flucytosine is not recommended in azotemic patients because of potentially lethal toxicity to the colon and bone marrow. Ketoconazole is no longer used.

Additional nonantimicrobial interventions such as routine peritoneal lavage, the use of fibrinolytic agents, and the instillation of intraperitoneal immunoglobulins have not proved beneficial and therefore serve no role in the management of peritoneal dialysis–associated peritonitis.[346] There is no benefit to stopping peritoneal dialysis when peritonitis is diagnosed, and its discontinuation may lead to complications such as injury to the peritoneal surface.[353]

Catheter Removal and Prevention

Removal of the catheter is necessary in 10% to 20% of patients (Table 74.7). The indications for catheter removal include persistent infection at the skin exit site or tunnel; fungal, fecal, or mycobacterial peritonitis; *P. aeruginosa* peritonitis; persistent peritonitis despite 5 days of treatment; recurrent peritonitis with the same organism; and catheter malfunction (e.g., poor flow). The catheter should also be removed in patients with intraperitoneal abscess. In the setting of relapsing peritonitis, a new catheter can be placed at the time of removal if the fluid is clear, but not when removed for recalcitrant or difficult-to-sterilize cases such as fungal infection. Use of oral or intraperitoneal antibiotics has not been shown to be effective in preventing peritonitis during peritoneal dialysis. An antibiotic given just before placement of the peritoneal catheter may decrease the incidence of peritonitis and wound infection. Antibiotic prophylaxis has been suggested for patients before extensive dental procedures (although peritonitis caused by dental flora is unusual) and before colonoscopy with biopsy or polypectomy. Also, it has been suggested with upper endoscopy and certain gynecologic procedures, including cervical and hysteroscopic biopsies and placement of intrauterine devices.[322,331] In addition, topical mupirocin applied to the exit site or intranasal application of mupirocin has been used to eliminate nasal carriage with *S. aureus* and has been shown to reduce exit site infections, but it has not yet been shown to significantly reduce the incidence of CAPD-related peritonitis.[354] Advances in CAPD instrumentation, such as titanium adapters, connector systems with disinfectant, and in-line filters, may decrease the frequency of peritonitis but add to the overall cost of CAPD.

Acute Peritoneal Dialysis

The incidence of peritonitis during acute peritoneal dialysis has remained stable since the 1980s. Innovations in technique, which began during the 1960s, reduced the rate of peritonitis from 50% to lower levels. These innovations included closed drainage systems, small-bore catheters, limitation of dialysis to no longer than 72 hours, incorporation of a Millipore filter into the tubing, and development of closed automatic systems. Use of dry-heat incubators to warm the dialysate also decreases the risk of contamination that may occur when water baths are used for this purpose.

Some authorities have recommended that cultures of dialysate be obtained every 8 to 24 hours during acute peritoneal dialysis and at its termination. Culture of dialysate from the last exchange is more useful than culture of the catheter tip at the end of dialysis because the catheter tip is frequently contaminated at the time of its removal. Results of these routine cultures, in the absence of symptoms or cloudy fluid, are of doubtful value for initiation of therapy. Of more importance, dialysate samples should be cultured and examined microscopically (cell count, Gram stain) if the dialysate becomes cloudy or if the patient develops signs or symptoms of peritonitis (e.g., fever, abdominal pain). Cultures are obtained best by syringe from the port closest to the catheter.

Antibiotic-resistant, hospital-acquired, gram-negative bacilli and staphylococci frequently cause peritonitis during acute peritoneal dialysis. It is recommended that therapy be initiated with intraperitoneal vancomycin and gentamicin (or tobramycin), with or without concurrent or subsequent parenteral infusion of the same antibiotics, depending on the severity of the illness and the response to initial therapy (see Table 74.6 for dosages). The antibiotic regimen should be modified when the culture results become available. The clinical manifestations, prognosis, and response to therapy are similar to those described previously for peritonitis associated with chronic peritoneal dialysis.

INTRAPERITONEAL ABSCESSES

Etiology

Intraperitoneal abscess can complicate either primary or secondary peritonitis. Diseases causing secondary intraperitoneal abscesses include appendicitis, diverticulitis, biliary tract lesions, pancreatitis, perforated peptic ulcers, inflammatory bowel disease, trauma, and abdominal surgery. The relative frequency of abscess formation associated with appendicitis may be declining, and the frequency of trauma and diverticulitis may be increasing.[355] The location of an abscess is generally related to the site of primary disease and the direction of dependent peritoneal drainage. Appendicitis has been reported to be associated most commonly with right lower quadrant and pelvic abscesses; colonic diverticulitis, with left lower quadrant and pelvic abscesses; and pancreatitis, with lesser sac abscesses. In one large series of 194 intraperitoneal abscesses in 1973,[356] about 44% were in the right lower quadrant, 14% in the left lower quadrant, and 14% in the pelvis, whereas 20% were perihepatic. In a 1983 series reported by Saini and associates,[357] the frequencies of various abscess locations had changed, perhaps reflecting the change in the relative frequency of the various etiologic diseases: subphrenic, 26%; pelvic, 20%; paracolic, 13%; periappendicular, 13%; retroperitoneal, 10%; hepatic, 7%; interloop, 4%; and lesser sac, 4%.

Of the various perihepatic (right subphrenic, right subhepatic, left perihepatic, and lesser sac) abscesses, the most common is in the right subphrenic space, but the difference in numbers between the right and left sides has been decreasing. In 1977, in one large series of 267 cases of intraabdominal abscesses, about half were in the subphrenic space, 60% of which were noted in the left perihepatic space.[358] This increased frequency of left perihepatic space abscess has also been noted more recently. That finding is in contrast to the series of Ochsner and DeBakey in 1939,[359] when right subphrenic abscesses were most common owing to the numerous ruptured appendices.

In children, appendicitis is still responsible for more than 50% of the cases of subphrenic abscess. In adults, perihepatic abscesses currently occur mainly as postoperative complications, rather than in neglected primary intraabdominal infections, such as appendicitis or perforated peptic ulcer. This fact may explain the increasing frequency of subphrenic abscess, especially on the left side, in comparison with other intraperitoneal sites.[358] Usually the surgery has been in the gastroduodenal and biliary tracts. One group of investigators[360] noted that abscesses that occurred after gastric operations were in the left subphrenic space if incidental splenectomy had been performed but in the right subhepatic space if splenectomy had not been performed. The subhepatic space is involved less frequently than the subphrenic spaces. Lesser sac abscesses usually follow pancreatitis or perforation of the stomach or duodenum. Multiple perihepatic space abscesses have been reported in 5% to 26% of the patients.[360]

Bacteriologic Findings

These infections are typically polymicrobial. In studies in which bacteriologic techniques permitted isolation of anaerobes, anaerobes were found in 60% to 70% of cases.[356,357,361] In one study, anaerobes were recovered in 20 of 24 subphrenic abscesses and *B. fragilis* was the most common pathogen; anaerobic cocci and clostridia were found in 50%

of the patients. Other bacteria frequently recovered are *E. coli, Klebsiella* and *Enterobacter* organisms, *Proteus* spp., *P. aeruginosa, S. aureus,* and enterococci.[356]

Pathogenesis

Intraperitoneal abscesses develop as a result of localization of diffuse peritonitis, usually in the pelvis, perihepatic spaces, and paracolic gutters. In addition, abscesses may develop around diseased organs (e.g., periappendiceal or pericholecystic abscesses) or after a penetrating wound (stabbing, gunshot, auto accident, or other trauma) or surgical procedure. These abscesses are termed *secondary* and account for most intraperitoneal cases. In contrast, the pathogenesis of primary abscesses is unknown and is presumably similar to that of primary peritonitis.

Clinical Manifestations

An acute course, with a high intermittent fever, shaking chills, abdominal pain, and tenderness over the involved area, is characteristic. The clinical pattern may be that of an acute secondary illness occurring after surgery for primary abdominal disease or a prolonged recuperative course in a patient who has been receiving antibiotics after abdominal surgery. Various authors[359,360] have emphasized the occasional chronicity of subphrenic abscesses and have speculated that the course is often modified by antibiotics. Subphrenic abscesses have been described with 6 months or more of an indolent illness.[362] Some patients may present with fever of unknown origin.

Local symptoms and signs vary widely with the location and source of the abscess. Subphrenic abscesses are usually accompanied by chest findings with costal tenderness and pleural or pulmonary involvement, whereas subhepatic abscesses have more dominant signs of upper abdominal or subcostal involvement and fewer pulmonary changes.

Diagnosis

Noninvasive diagnostic procedures, including ultrasonography and CT, have provided greater sensitivity and specificity than have routine radiography and radionuclide scanning.[363] These latter techniques are occasionally useful, however, and sometimes a combination of diagnostic tests is the optimal approach to confirm the diagnosis of intraabdominal abscess.

Plain radiographs of the abdomen can suggest the location of abscesses in 50% of patients.[364] Radiologic findings associated with a subphrenic abscess may include pleural effusion, elevation of the hemidiaphragm, or loss of diaphragmatic movement at fluoroscopy. Routine radiography also may reveal displacement of viscera by an abscess. These findings can be enhanced with contrast media. The stomach may be outlined with barium or air to indicate displacement caused by a left perihepatic or lesser sac abscess. The presence of gas, either as a single air-fluid level or as mottling within the abscess, may aid in localization on routine abdominal radiography.

Leukocytes tagged with gallium 67 and indium 111 are used in radionuclide scans, which at times may be helpful in detecting intraabdominal abscesses, although they have been largely supplanted by CT and MRI. In contrast to the technetium 99m sulfur colloid liver-spleen scan, which visualizes the entire organ and delineates abnormal areas as "cold" spots caused by decreased uptake of the isotope, gallium 67–tagged and indium 111–tagged leukocytes accumulate in areas of inflammation, such as abscesses, and appear as areas of increased radioactivity or "hot" spots.[365] Gallium is excreted into the intestinal tract and can accumulate in any inflammatory process and in certain neoplasms. For these reasons, false-positive scan readings can occur when radioactivity within the lumen of the bowel, within the wall of an inflamed bowel, or within a noninfected operative site in the process of healing is misinterpreted as an intraabdominal abscess.

Indium 111–tagged leukocyte scans are as sensitive as but more specific than gallium 67–tagged scans. The labeled leukocytes tend to concentrate only in areas of inflammation because, in contrast to gallium 67, indium 111 is not secreted into the bowel.[366] Abscesses in the liver and spleen may be difficult to detect solely on gallium 67–tagged or indium 111–tagged leukocyte images because normal accumulation of activity in these organs may mask an adjacent inflammatory focus. This problem can be overcome by comparing gallium 67 or indium 111 images with technetium 99m scans.

Ultrasonography is a noninvasive technique that is helpful in the determination of the size, shape, consistency, and anatomic relationships of an intraabdominal mass. The appearance of abscesses may vary widely from echo-free lesions to highly echogenic masses, but they typically appear as a fluid collection with an irregular wall and the presence of a few internal echoes. Ultrasound images may be obscured by overlying gas-filled viscera and by postoperative wounds and drains.

CT has proved especially well suited for the diagnosis of intraabdominal abscess.[367,368] Definition is unimpeded by intraluminal gas and postoperative changes except in the presence of surgical metallic clips or residual barium that may disrupt the image. Observed findings consistent with abscess include a low-density tissue mass and a definable capsule (Fig. 74.4). CT can reveal extraluminal gas, a finding highly suggestive of abscess. Contrast material is commonly administered orally and intravenously in attempts to diagnose intraabdominal abscess. The

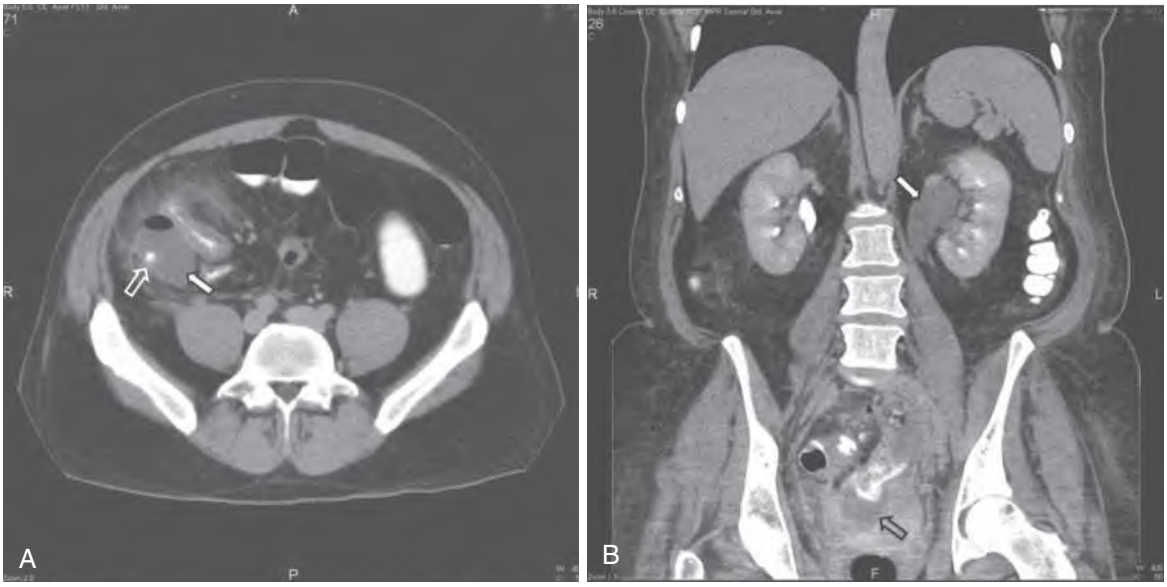

FIG. 74.4 Computed tomographic scans of abdomen and pelvis after administration of oral and intravenous contrast medium. (A) Perforated appendicitis: right lower quadrant collection with an air-fluid level *(solid arrow)* surrounding a dilated appendix *(open arrow).* (B) Perforated diverticulitis associated with abscess *(open arrow),* producing obstructive hydronephrosis *(solid arrow).*

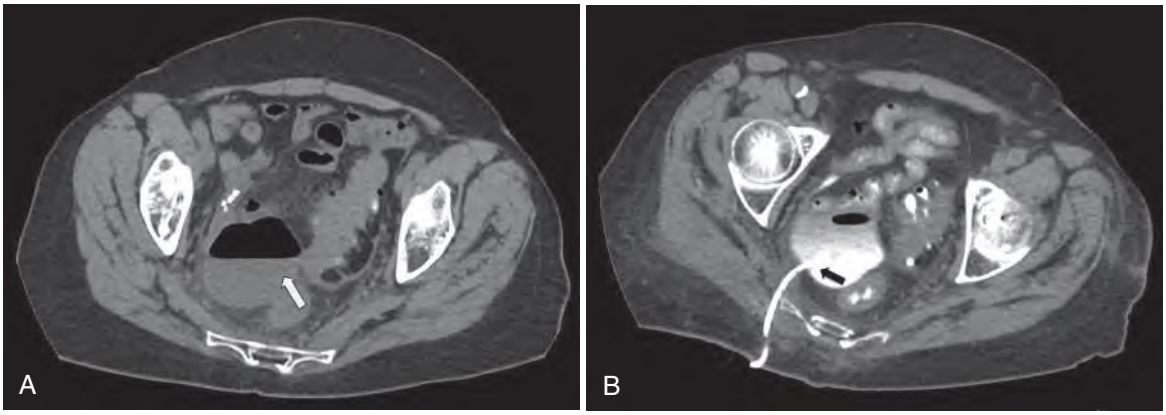

FIG. 74.5 Computed tomographic scans of abdomen-pelvis. (A) Perforated diverticulitis: pelvic collection with an air-fluid level *(white arrow).* (B) Same patient after interventional percutaneous drain placement of the diverticular abscess *(black arrow).*

intraluminal contrast material helps to distinguish loops of bowel from abscess cavities, and the parenteral contrast material may enhance a surrounding capsule, allowing for easier identification.

MRI has the potential to display normal anatomy and to reveal abnormal conditions in many of the body's organ systems and anatomic regions.[369,370] Only a few trials have compared MRI with older radiologic procedures. In one study, MRI more clearly delineated the extent of inflammatory changes than did CT, and it distinguished the abscess better from the surrounding structures.[371] In addition, the use of MRI does not require the administration of contrast medium and eliminates exposure to radiation, but it may be more costly than radiologic techniques.

Arteriographic localization has also been helpful. Overreliance on any one of these techniques is dangerous, and results should be confirmed with other methods and the clinical findings.

Prognosis

The period of morbidity is unusually prolonged in patients with intraperitoneal abscesses. Altemeier and colleagues[356] reported average hospital stays of 21 to 47 days. The presence of residual recurrent infection caused by inadequate surgical drainage, more common in patients with multiple or bilateral abscesses, is associated with significantly greater mortality.

Therapy

The main therapy for any intraperitoneal abscess is drainage. Effective management depends on accurate localization of the abscess, discrimination between single and multiple abscesses, and early and adequate drainage. Conventional therapy for intraperitoneal abscesses usually has included surgical drainage. Since the 1980s, successful therapy has been accomplished with percutaneous catheter drainage as an alternative to surgery (Fig. 74.5).[372–375] This method has become possible with the use of refined imaging techniques, especially ultrasonography and CT.[376]

The general requirements for CT-guided or ultrasonography-guided percutaneous catheter drainage include (1) an abscess that can be approached adequately via a safe percutaneous route; (2) an abscess that is unilocular; (3) an abscess that is not vascular and the absence of coagulopathy; (4) joint radiologic and surgical evaluation, with surgical backup for any complication or failure; and (5) the possibility of dependent drainage through the percutaneously placed catheter.[315] CT also allows detection of an unsuspected additional intraabdominal problem that would otherwise necessitate surgical intervention. Percutaneous catheter drainage can be used as an initial approach in a patient too unstable to withstand immediate surgery. Definitive surgery can be postponed until the patient is in better condition. Percutaneous drainage of peridiverticular or appendiceal abscesses may permit a subsequent one-stage procedure of primary resection and immediate anastomosis, rather than the more costly and complicated multistage procedure.[377–379] After percutaneous placement of the catheter with CT or ultrasound guidance and aspiration of the abscess cavity, the catheter is placed for drainage by gravity or low suction until the daily drainage volume is minimal. Clinical response and collapse of the abscess cavity, evident on repeat scanning, should follow successful drainage. Some patients with percutaneous catheter drainage can be managed at home with their catheters in place. In 80% to 90% of the patients who fit these criteria, percutaneous drainage has been successful.[373] Attempts at drainage of loculated, poorly organized, multiple, or extensive collections are less successful. In most series, the frequency of complications ranges from 5% to 15%,[372] including septicemia, hemorrhage, peritoneal spillage, and fistula formation. In addition, failure may occur because of undrained abscesses or pus too viscid to drain via the catheter. Reports indicate that the morbidity and mortality associated with percutaneous drainage may be lower than with surgical treatment.[380]

Antimicrobial therapy should be started immediately after appropriate specimens (e.g., blood) are obtained for culture; usually they are obtained before drainage. Because the pathogens are usually similar to those involved in secondary peritonitis, initial antibiotic therapy is directed similarly at the anaerobes, especially *B. fragilis* and the Enterobacteriaceae. The antimicrobial regimens discussed in the section on treatment of secondary peritonitis should be appropriate initial therapy (see Table 74.5). This antibiotic regimen should be adjusted to conform to results of in vitro testing of the infecting organisms isolated from blood or purulent material obtained at surgery or from catheter drainage. During the course of a prolonged illness, repeated cultures of blood and purulent collections, when clinically indicated, should provide a basis for change in antimicrobial therapy.

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The complete reference list is available online at Expert Consult.

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75 Infections of the Liver and Biliary System (Liver Abscess, Cholangitis, Cholecystitis)

Costi D. Sifri and Lawrence C. Madoff

SHORT VIEW SUMMARY

Definition
- A pyogenic liver abscess is the end result of a number of pathologic processes resulting in a focal, purulent bacterial collection in the liver.
- An amebic liver abscess is an invasive complication of intestinal amebiasis resulting in a focal collection of nonpurulent fluid in the liver.
- Cholecystitis is inflammation/bacterial infection of the gallbladder often resulting from obstructing gallstones. Acalculous cholecystitis is a similar process in the absence of gallstones.
- Cholangitis is inflammation/infection of the bile ducts.

Epidemiology
- An estimated 1 to 4 cases of pyogenic liver abscess occur per 100,000 persons each year.
- Amebic liver abscesses are rare—about 1 case per million persons annually in the United States—but are more common in endemic regions. They affect men about 10 times more frequently than women.
- Tens of millions in the United States have gallstones; 1% to 3% are complicated by acute cholecystitis.
- Approximately 120,000 cholecystectomies occur each year in the United States.
- Between 2% and 15% of cases occur without gallstones, known as "acalculous cholecystitis."
- In endemic regions, parasites such as *Ascaris* and *Clonorchis* may cause biliary disease.

Microbiology
- Pyogenic liver abscesses may be monomicrobial, especially when caused by bacteremia, or polymicrobial, involving aerobic gram-negative bacilli and anaerobes.
- Hypermucoviscous *Klebsiella pneumoniae* (typically K1 and K2 strains) are now an important cause of pyogenic liver abscess, particularly in parts of Asia but increasingly elsewhere.
- Amebic liver abscesses are caused by invasive strains of *Entamoeba histolytica.*

Diagnosis
- Symptoms are often nonspecific, and a high index of suspicion is required.
- Diagnostic imaging, especially by ultrasonography, radionuclide cholescintigraphy, computed tomography, or magnetic resonance imaging, is essential. For pyogenic liver abscesses, it is often coupled with diagnostic/therapeutic aspiration.

Therapy
- Some pyogenic processes require prompt recognition and urgent image-guided drainage or definitive surgery.
- Antibiotics directed at the suspected pathogens play an important role as adjuncts to surgery, or, in limited cases, they may be the sole form of therapy, (e.g., small pyogenic liver abscesses [see Tables 75.4 and 75.6], amebic liver abscess).

LIVER ABSCESS

Liver abscesses fall broadly into two categories: amebic and pyogenic. Amebic liver abscess represents a distinct clinical entity caused by invasive *Entamoeba histolytica* infection. It has a distinct pathogenesis that is characterized by the specific induction of hepatocyte apoptosis by the organism. Further discussions of the epidemiology, genetics, and biology of *E. histolytica* and of intestinal amebiasis can be found elsewhere in this volume (see Chapters 98 and 272). Pyogenic liver abscess, by contrast, does not represent a specific liver disease but is the end result of a number of pathologic processes that cause a suppurative infection of the liver parenchyma.

Epidemiology/Etiology

Amebic Liver Abscess

In the United States, amebic liver abscess has become a rare disease that is found almost exclusively in travelers and immigrants. In 1994, the last year in which incidence data were collected, there were only 2983 cases of amebiasis; the percentage of cases complicated by abscess is unknown, but it is probably well under 10%, roughly 1 case per million persons per year.[1] Worldwide, contamination of food and drinking water has maintained *E. histolytica* infection second only to malaria as a cause of death from parasitic disease. The epidemiology of this disease has been greatly informed by the appreciation that a closely related nonpathogenic species, *Entamoeba dispar,* colonizes between 5% and 25% of persons.[2,3] *E. dispar* has no apparent propensity for invasive disease, even among patients with acquired immunodeficiency syndrome (AIDS). In industrialized countries, most asymptomatic individuals with *Entamoeba* in their stool are colonized with *E. dispar,* whereas in highly endemic regions, asymptomatic infection with *E. histolytica* may exceed the rate of *E. dispar* colonization.[4–11] In addition, other *Entamoeba* species have been identified; these include *Entamoeba moshkovskii,* which causes noninvasive diarrhea, and *Entamoeba bangladeshi,* which is of unknown virulence. Because these species are indistinguishable by light microscopy, the presence of *Entamoeba* in the stool is not sufficient to establish the cause of a liver abscess. Men and women experience equivalent rates of *E. histolytica* infection, but adult men are at a 10-fold higher risk for invasive disease (colitis or extracolonic disease) than other populations.[12] The reason for this disparity remains uncertain, although gender differences in complement-mediated killing of *E. histolytica* and cytokine responses to amebic liver infection have been proposed.[13,14] In addition, testosterone has been shown to be a risk factor for the development of amebic liver abscesses in experimental animals.[15,16]

Pyogenic Liver Abscess

The incidence of pyogenic liver abscess is about 1 to 4 cases per 100,000 individuals annually in the United States and Europe.[17–20] This incidence has been relatively stable, with a slight increasing trend in more recent case series that may reflect changes in the true incidence or improved detection.[19] In Asia, the incidence of pyogenic liver abscess may be 5- to 10-fold higher and is associated with the emergence of community-acquired *Klebsiella pneumoniae* infection.[21,22] Pyogenic liver abscess is a disease of middle-aged persons, with a peak incidence in the fifth and sixth decades of life; this pattern mirrors the prevalence in the population of biliary disease, which is now the major cause of pyogenic liver abscess. No significant sex, ethnic, or geographic differences seem to exist in disease frequency, in contrast to the epidemiology of amebic liver abscess. About one-half of patients have a solitary abscess. Right-sided

abscesses are most common, followed by left-sided abscesses and then abscesses involving the caudate lobe. This distribution probably reflects the relative mass of each lobe, although more complicated explanations, such as patterns of hepatic blood flow, have been proposed.

Pathogenesis and Pathophysiology

Amebic Liver Abscess

Infection with *E. histolytica* results from ingestion of cysts in fecally contaminated food or water. Excystation occurs in the intestinal lumen, and trophozoites migrate to the colon, where they adhere by means of a lectin that specifically binds galactose *N*-acetyl-D-galactosamine (the Gal/GalNAc lectin) on colonic epithelium and multiply by binary fission.[23,24] At high densities, trophozoite encystation is initiated, and newly formed cysts are released into the stool to complete the life cycle. Most individuals experience asymptomatic infection, but approximately 10% develop symptomatic colitis when invasion of the colonic mucosa occurs. Spread to the liver via the portal system occurs in less than 1% of cases.[2] A number of virulence factors have been implicated in the development of amebic liver abscess, including small proteins (amoebapores) that punch holes in lipid bilayers of target cells, cysteine proteases, and the Gal/GalNAc lectin.[25–31] *E. histolytica* induces apoptosis in hepatocytes and neutrophils, forming large, nonpurulent, "anchovy paste" abscesses that grow inexorably without treatment.[32,33] The mechanism by which *E. histolytica* induces apoptosis is unknown, but its importance is underscored by the resistance of caspase-3–deficient mice to amebic liver abscess formation.[34,35] Recently, an *E. histolytica* surface protein that participates in apoptotic corpse phagocytosis, the phagosome-associated transmembrane kinase (PATMK), was shown to be required for intestinal amebiasis in a murine infection model; however, PATMK was found to not contribute to the development of experimental amebic liver abscess.[36] By contrast, amoebapore expression was found to be required for the formation of liver abscesses but not amebic colitis.[29] These findings suggest that the contribution of particular amebic virulence factors to pathogenesis may be tissue specific, and many of these factors have been recently reviewed.[37]

Predisposition to liver disease is influenced by host genetics. In studies of Mexican mestizo children and adults, individuals with the major histocompatibility complex haplotype HLA-DR3 have an increased frequency of amebic liver abscess compared with healthy populations of the same socioeconomic background.[38,39] Host factors thought to be critical in the containment and clearance of invasive amebae include complement, neutrophils, interferon-γ, nitric oxide, and adaptive immune responses (see Chapter 272).[13,14,40–44]

Pyogenic Liver Abscess

Pyogenic liver abscess does not represent a distinct pathophysiologic process but occurs whenever the initial inflammatory response fails to clear an infectious insult to the liver. Pyogenic liver abscesses are usually classified by presumed route of hepatic invasion: (1) biliary tree, (2) portal vein, (3) hepatic artery, (4) direct extension from contiguous focus of infection, and (5) penetrating trauma. Ideally, this approach defines the microbiology of the abscess and therefore guides empirical antibiotic choice, but it is limited by the high frequency of cryptogenic abscesses. The frequencies of the presumed routes of hepatic invasion are presented in Table 75.1.[18,45–76]

TABLE 75.1 Frequency of Route of Infection in Hepatic Abscess

ROUTE OF INFECTION	FREQUENCY (%)
Biliary tree	40–50
Hepatic artery	5–10
Portal vein	5–15
Direct extension	5–10
Trauma	0–5
Cryptogenic	20–40

Modified from references 17, 18, 42–45, and 46–71.

1. *Biliary tree.* Cholangitis (discussed later) is now the major identifiable cause of pyogenic liver abscess. In such cases, multiple abscesses are usually present and anaerobes are infrequent. The underlying biliary obstruction is usually a result of gallstone disease, but it can also be caused by an obstructing tumor, an occluded stent, overwhelming cryptosporidiosis, or *Ascaris lumbricoides* migration into the biliary tree.
2. *Hepatic artery.* Any systemic bacteremia (e.g., endocarditis, line sepsis) can spread to the liver via this route. Patients who die of overwhelming sepsis frequently have extensive microabscess formation in their livers at autopsy, but macroscopic liver abscess formation in patients who recover from septic shock is uncommon, underscoring the capacity of the liver to clear even large insults.
3. *Portal vein.* The portal venous system drains almost all of the abdominal viscera. Pylephlebitis from diverticulitis, pancreatitis, omphalitis, inflammatory bowel disease, or postoperative infection can result in pyogenic liver abscess. Untreated appendicitis was historically a major cause in this category but was greatly diminished in importance with the introduction of antibiotics.
4. *Direct extension from a contiguous focus of infection.* This may occur with cholecystitis or subphrenic, perinephric, or other intraabdominal abscesses.
5. *Trauma.* Any penetrating trauma to the liver, even as subtle as ingestion of a toothpick, can result in abscess formation. Blunt trauma can also predispose to pyogenic liver abscess formation, presumably because of hepatic hematoma formation and subsequent increased risk of seeding by bacteria. Similarly, hepatic destruction from sickle cell disease, tumor necrosis (either spontaneous or following iatrogenic embolization), or cirrhosis can predispose to abscess formation.

Host factors that predispose to abscess formation from "routine" hepatic bacterial insults may be present in many cryptogenic abscesses. Systemic illness such as diabetes mellitus, cardiopulmonary disease, malignancy, and cirrhosis are common in patients with liver abscesses and may be predisposing factors. Diabetes was shown in one retrospective study to impart a greater than threefold risk of development of pyogenic liver abscess.[77] Conditions of neutrophil dysfunction are associated with a marked predisposition for abscesses of the liver and elsewhere. For example, one-third of patients with chronic granulomatous disease followed at the National Institutes of Health Clinical Center over four decades developed pyogenic liver abscesses; 47% had recurrent abscesses.[78] Finally, hemochromatosis conveys a particular susceptibility to abscesses caused by *Yersinia enterocolitica*.[79]

Microbiology

Amebic Liver Abscess

Although *E. histolytica* is the only species of *Entamoeba* known to cause invasive infections, certain strains may be more proficient at causing liver disease than others. In surveys of clinical *E. histolytica* isolates, genetically distinct strains recovered from amebic liver abscesses were infrequently found to cause asymptomatic intestinal colonization or intestinal disease.[80,81] More recently, Ali and colleagues[82] analyzed paired isolates from patients with concurrent amebic liver abscesses and intestinal infection. In all cases, the liver and intestinal amebae had discordant genotypes, suggesting either that amebae undergo genetic reorganization during invasion or that only a subset of strains is capable of metastasizing to the liver.

Pyogenic Liver Abscess

In light of the diverse pathologic processes that have been discussed, it is understandable that sweeping generalizations about the microbiology of pyogenic liver abscess are difficult. The picture is further complicated because abscess material is rarely obtained before the administration of antibiotics. Even in the preantibiotic era, a high rate of sterile cultures was seen, probably reflecting inadequate culture techniques. Despite these difficulties, abscess cultures are positive in 80% to 90% of cases.

TABLE 75.2 Microbiology of Liver Abscess

TYPE OF ORGANISM	COMMON (>10%)	UNCOMMON (1%–10%)
Gram-negative	*Escherichia coli* *Klebsiella* spp.	*Pseudomonas* *Proteus* *Enterobacter* *Citrobacter* *Serratia*
Gram-positive	*Streptococcus* (anginosus group) *Enterococcus* spp. Other viridans-group streptococci	*Staphylococcus aureus* β-Hemolytic streptococci
Anaerobic	*Bacteroides* spp.	*Fusobacterium* Anaerobic streptococci *Clostridium* spp. Lactobacilli

The demonstration of anaerobic organisms in 45% of pyogenic liver abscesses by Sabbaj and colleagues[83] in 1972 led to an increased awareness of fastidious pathogens, and in recent case series, anaerobes were recovered 15% to 30% of the time.[a] Some of this decrease in the isolation of anaerobic organisms is probably attributable to the emergence of biliary tract disease as the major underlying cause of pyogenic liver abscess, but because of the difficulty in obtaining adequate culture data, these should be viewed as minimum estimates. There has also been an increased appreciation that many liver abscesses are polymicrobial, with estimates ranging from 20% to 50%, depending on the case series. If the source of the abscess is considered, abscesses with a biliary source are most likely to be polymicrobial, and cryptogenic abscesses are most frequently monomicrobial.[61] Some observers have noted that solitary abscesses are more likely to be polymicrobial than are multiple ones.[54,55] Although this has not been universally observed[61] and the small size of these studies prevents conclusive statements, it does suggest two alternative mechanisms for abscess formation. In the first, a synergistic combination of organisms converges by chance to form a single abscess, and in the second, a highly pathogenic organism forms abscesses wherever it was seeded.

In terms of specific pathogens (Table 75.2), *Escherichia coli* and *K. pneumoniae* are by far the most common isolates. The latter has been increasingly recognized as a cause of community-acquired monomicrobial liver abscesses (discussed later). Enterococci and viridans-group streptococci are also common, primarily in polymicrobial abscesses. *Staphylococcus aureus,* by contrast, is more commonly associated with monomicrobial abscesses. Although pyogenic liver abscesses due to fungi, particularly *Candida* species, have been reported, they are comparatively rare and are excluded from most case series.

16S ribosomal RNA sequencing may be a useful technique to identify the etiologic agent in instances in which cultures are negative. In a cohort of 20 Korean patients, only 45% of abscess fluid bacterial cultures were positive, compared with 90% of samples tested using 16S ribosomal RNA sequencing. Of interest, all samples were found to contain sequences of unknown bacteria.[84] Whether these unknown organisms play a role in the pathogenesis of pyogenic liver abscess remains to be determined.

Epidemic *Klebsiella pneumoniae* Pyogenic Liver Abscess

In the mid-1980s, investigators in Taiwan first noted a distinctive syndrome of monomicrobial *K. pneumoniae* pyogenic liver abscess in individuals who were often diabetic but had no biliary tract disorders.[85–87] Subsequently, community-acquired *K. pneumoniae* liver abscess has become a major health problem in parts of Asia, accounting for 80% of all cases of pyogenic liver abscess in Taiwan and South Korea,[88–90] and has been reported sporadically elsewhere in Asia, North America, Europe, Africa, and Australia, initially in persons of Asian ethnicity (raising the possibility of genetic predisposition), but more recently also in individuals of non-Asian descent.[90–97] Although mortality rates for epidemic *K. pneumoniae* liver abscess are generally low, metastatic infections such as meningitis and endophthalmitis occur in 10% to 16% of all cases.[98–100] Not surprisingly, *K. pneumoniae* has also become a frequent cause of pylephlebitis in this region.[101]

Infections are primarily caused by hypermucoviscous strains of *K. pneumoniae* of the capsular K1 (or occasionally K2) serotype.[98,99] Chuang and colleagues[102] have identified a 25-kb chromosomal element containing 20 open reading frames that directs K1 capsular polysaccharide synthesis (CPS). Mutagenesis of one *cps* gene, *magA* (for mucoviscosity-associated gene A), abolishes hypermucoviscosity, increases sensitivity to phagocytosis and serum-mediated lysis, and reduces virulence in mice.[103] *magA* can also be used as a genetic marker for invasive serotype K1 *K. pneumoniae* strains. Epidemic hypermucoviscous strains of *K. pneumoniae* often produce other virulence determinants, including the regulator of mucoid phenotype protein RmpA and the iron-acquisition system aerobactin, encoded on a 170- to 180-kb large virulence plasmid (pLVPK) not typically found in other *K. pneumoniae* strains.[104] Isolates are characteristically highly drug sensitive, but recent outbreaks of often fatal ventilator-associated pneumonia in China due to carbapenemase-producing hypermucoviscous *K. pneumoniae* raise the specter of life-threatening, highly drug-resistant *K. pneumoniae* infections not only in hospitals, but potentially in the community.[105]

TABLE 75.3 Signs and Symptoms of Liver Abscess

FEATURE	AMEBIC LIVER ABSCESS[16,46–75,117]	PYOGENIC LIVER ABSCESS[17,72,106–115]
Epidemiology		
Male-to-female ratio	5–18	1–2.4
Age (yr)	30–40	50–60
Duration (d)	<14 (≈75% of cases)	5–26
Mortality (%)	10–25	0–5
Symptoms and Signs (Approximate % of Cases)		
Fever	80	80
Weight loss	40	30
Abdominal pain	80	55
Diarrhea	15–35	10–20
Cough	10	5–10
Jaundice	10–15	10–25
Right upper quadrant tenderness	75	25–55
Laboratory Tests (Approximate % of Cases)		
Leukocytosis	80	75
Elevated alkaline phosphatase	80	65
Solitary lesion	70	70

Clinical Manifestations

Amebic Liver Abscess

Patients with amebic liver abscess typically present with fever and a dull, aching pain localizing to the right upper quadrant, but jaundice is rare. Only 15% to 35% of patients present with concurrent gastrointestinal symptoms, including nausea, vomiting, abdominal cramping, and diarrhea (Table 75.3).[18,46–75,106–113] Symptoms are acute (<2 weeks' duration) in about two-thirds of cases but can develop months to years after travel to an endemic area.[2,3] The presentation is indistinguishable from pyogenic liver abscess on clinical grounds, and a careful search for epidemiologic risk factors is of paramount importance. Corticosteroid use and male sex are well-established risk factors for invasive amebic disease.[12,106]

Pyogenic Liver Abscess

Only 1 patient in 10 presents with the classic triad of fever, jaundice, and right upper quadrant tenderness. Fever is common, often without localizing signs but only with a general failure to thrive, including malaise,

[a]References 18, 52–54, 57, 65, 69, 70, 72, and 76.

fatigue, anorexia, or weight loss (see Table 75.3). When present, localizing symptoms such as vomiting or abdominal pain are not specific. The duration of symptoms before presentation varied widely in most case series, and there was seldom agreement on an average duration. Butler and McCarthy[48] attempted to address this issue by stratifying according to acute and chronic presentations. They found the former to be typically associated with acute, identifiable abdominal pathology such as cholangitis or appendicitis, whereas abscesses that presented chronically were often cryptogenic. Other series support an association between etiology and chronicity. For example, Seeto and Rockey[61] found that hematogenous liver abscesses presented most acutely (3 days), and those secondary to pylephlebitis had the longest duration of symptoms (42 days).

Diagnosis

The diagnosis of liver abscess should be suspected in all patients with fever, leukocytosis, and a space-occupying liver lesion. Because of the nonspecific symptoms on presentation, the initial clinical impression is frequently wrong and may include cholangitis, pneumonia, hepatic malignancy, intraabdominal catastrophe, or pneumonia.[50] Before the widespread use of noninvasive imaging, liver abscess was among the most frequently identifiable causes of fever of unknown origin. Leukocytosis is present in most patients; recent studies[69,70,73–75,77,114,115] report leukocytosis in 68% to 88% of all patients, with mean white blood cell counts of 15,000 to 17,000/mm.[3] An elevated alkaline phosphatase concentration is the most frequently abnormal liver function test, occurring in about two-thirds of patients with liver abscess, but a normal value does not exclude the diagnosis. Abnormalities of alanine aminotransferase, aspartate aminotransferase, and bilirubin are generally small, although they may be more pronounced in some patients with biliary disease. Albumin concentration and prothrombin time tend to be normal or nearly so. Procalcitonin levels are typically elevated. Chest radiographs are abnormal about half of the time but are of no real value in making the diagnosis. Therefore, although laboratory studies may suggest liver abnormalities, they are of no use in making the diagnosis of pyogenic liver abscess, and a high index of suspicion is required if the diagnosis is to be made in a timely fashion. Laboratory abnormalities may be of prognostic significance, most likely as markers of comorbidities. A multivariate analysis of risk factors found that a hemoglobin concentration of less than 10 g/dL and a blood urea nitrogen concentration greater than 28 mg/dL were independent predictors of mortality in patients found to have pyogenic liver abscess (odds ratios of 13 and 14, respectively).[65]

Once the diagnosis is suspected, radiographic imaging studies are essential to diagnose pyogenic liver abscess.[66] Ultrasonography and computed tomography (CT) scanning have proved particularly useful for demonstration and drainage of abscesses. Ultrasonography is the study of choice in patients with suspected biliary disease and in those who must avoid intravenous contrast or radiation exposure; it has a sensitivity of 70% to 90%. Contrast-enhanced CT scanning has improved sensitivity (≈95%) and is superior for guiding complex drainage procedures. Intravenous contrast is required for optimal imaging in two-thirds of patients.[116] Magnetic resonance imaging (MRI) studies are seldom required, but they may be better at distinguishing abscesses from noninfectious liver lesions such as neoplasia. Fine-needle aspiration is the definitive diagnostic procedure, and MRI is a cumbersome tool for guiding drainage procedures.

In patients with pyogenic liver abscess, blood cultures are positive about half of the time. It is imperative that multiple sets of anaerobic and aerobic cultures be obtained because these are frequently the only cultures obtained before antibiotic administration, and in about 7% of cases they are the only positive culture data obtained.[54,61,73] The diagnosis ultimately rests on obtaining purulent material from an aspiration of the abscess cavity, usually under radiographic guidance. Failure to obtain the expected pus should prompt a reevaluation of the differential diagnosis, considering liver cyst, malignancy, and amebic liver abscess. Purulent material should always be sent for Gram stain, which may provide the only clue to a mixed infection in patients heavily treated with antibiotics. The importance of prompt delivery of anaerobic specimens under proper conditions cannot be stressed enough.

Patients with amebic liver abscess classically present with a single large abscess in the right lobe of the liver, but the abscess can be anywhere and multiple lesions are not infrequent. Moreover, there is near-complete overlap in the symptomatology of the two diseases (see Table 75.3). A Spanish study found that age 45 or younger, presence of diarrhea, and a solitary right lobar abscess favored amebic etiology.[117] Distinguishing amebic from pyogenic liver abscess is not possible with the use of clinical criteria alone; however, a presumptive diagnosis of amebic liver abscess can be made in a patient with positive serology and a space-occupying liver lesion on CT or ultrasonography. Serum amebic serology by enzyme immunoassay has a sensitivity of about 95% and is highly specific for *E. histolytica* infection, especially in persons from nonendemic areas.

While *E. histolytica* serology can be negative in a minority of acute presentations (symptom duration <2 weeks), a repeat serology determination is usually positive.[118–121] It should be remembered that a positive serology result only confirms present or prior *E. histolytica* infection and cannot distinguish colitis from extraintestinal disease. Antigen detection represents a complementary diagnostic method. A commercially available enzyme-linked immunosorbent assay (ELISA) that detects the Gal/GalNAc lectin has been shown to be positive in more than 95% of serum samples and about 40% of stool or abscess specimens in patients with amebic liver abscess.[122,123] Several other US Food and Drug Administration (FDA)–approved ELISA antigen detection assays are also available, but some may cross-react with *E. dispar.*[124,125] Microscopic examination of the stool for cysts is of little value because *E. histolytica* cannot be distinguished from *E. dispar.* Examination of aspirated liver abscess pus is also not recommended, given that trophozoites are identified in only 11% to 25% of cases.[122,126]

There is growing interest in new diagnostic technologies for amebic liver abscesses.[127,128] While nucleic acid amplification of fecal specimens (in the form of FDA-approved molecular multiplex panels for enteric pathogens) is a highly sensitive method for the diagnosis of amebic colitis,[129] patients with amebic liver abscesses generally do not have concurrent intestinal *E. histolytica* infection.[130] Polymerase chain reaction has been shown to be a potential diagnostic tool for aspirated pus or other body fluids from patients with amebic liver abscess, but its use is currently limited to research laboratories.[125,128,130–133] Some investigators have argued that in areas of low endemicity, suspected amebic liver abscess should be aspirated to exclude pyogenic liver abscess. Certainly, if there is no response to initial therapy, the abscess should be aspirated to confirm the diagnosis and to exclude pyogenic liver abscess. Bacterial superinfection of amebic liver abscess has been described in about 1% to 5% of cases, frequently as a complication of drainage procedures.[134]

Echinococcal cysts of the liver, which typically do not cause fever or tenderness, are distinguishable from amebic and pyogenic abscesses by CT but require separate consideration for aspiration (see Chapter 289).

Therapy

Amebic Liver Abscess

Amebic liver abscess can almost always be treated with medical therapy alone. Metronidazole (750 mg three times daily) is typically given for 7 to 10 days.[2,3] An alternative, tinidazole (2 g daily for 3 days), has been used extensively in Europe and the developing world and has been approved for use in the United States for the treatment of amebiasis.[135] Other nitroimidazoles with extended half-lives that are efficacious include secnidazole and ornidazole; neither drug is approved in the United States for treatment of amebic liver abscess, although secnidazole recently received FDA approval for the treatment of bacterial vaginosis in adult women. Decreased fever and abdominal pain are usually observed within 3 to 5 days after initiation of therapy. Patients frequently remain colonized with *E. histolytica* despite nitroimidazole treatment and should be treated with paromomycin, a nonabsorbable aminoglycoside with *E. histolytica* activity, to eliminate this condition.[136,137] It is generally accepted that uncomplicated amebic liver abscess does not require drainage. Percutaneous image-guided aspiration has replaced surgical drainage and should be employed if there is no response to appropriate therapy or the diagnosis is uncertain, to exclude pyogenic liver abscess and bacterial superinfection. Drainage should also be considered for large lesions at risk for rupture, particularly left-sided abscesses that can rupture into the

pericardium.[127] Percutaneous drainage has not been demonstrated to shorten hospital stay or to hasten clinical improvement, with the exception of one randomized controlled trial that found a salutary effect in patients with large abscesses (>300 mL).[107,138–143]

Pyogenic Liver Abscess

Unlike amebic liver abscess, pyogenic liver abscesses usually require drainage in addition to antibiotic therapy. Surgical drainage was traditionally the treatment of choice and, in the preantibiotic era, the only hope for cure. As early as 1953, McFadzean and associates[144] reported the use of percutaneous drainage with antibiotic therapy to treat 14 patients with liver abscess. After ultrasonography and CT became widely available, multiple studies confirmed this approach and made image-guided drainage procedures the preferred primary therapy, although some still advocate surgical drainage (Fig. 75.1). Surgical intervention should be considered if percutaneous drainage fails or management of concurrent intraabdominal disease is required, and also for some patients with multiple large or loculated abscesses.[145,146] Percutaneous catheter drainage

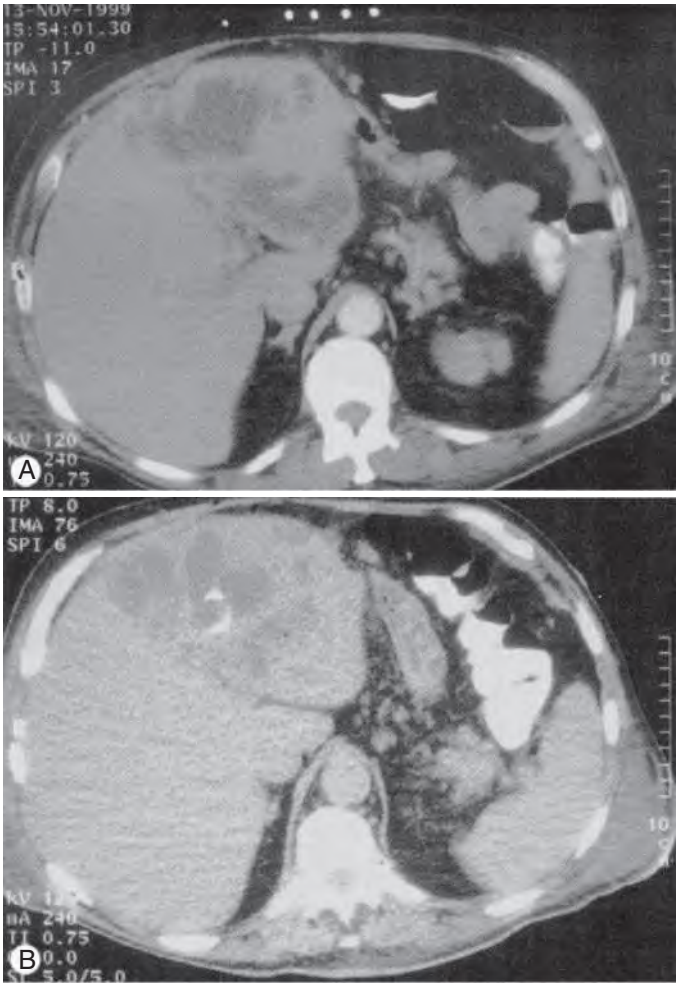

FIG. 75.1 Drainage of liver abscesses by percutaneous aspiration guided by computed tomography (CT). A 67-year-old man with a history of diabetes mellitus and rheumatoid arthritis and a distant history of a Billroth II gastric resection, recently diagnosed with adenocarcinoma of the stomach, presented with fever. A blood culture grew *Escherichia coli*. The liver was imaged by CT (A), revealing multiple hypodense lesions in the right hepatic lobe. The lesion was aspirated under radiologic guidance, and more than 500 mL of frank pus were drained. Cultures produced *E. coli* and several anaerobic bacterial species. Cytologic findings were consistent with metastatic adenocarcinoma. A radiodense percutaneous drainage catheter was left in place (B), and the patient was treated with intravenous antibiotics and continued drainage. Note the position of the catheter and the decrease in size of the abscess. *(Courtesy Lindsey Baden, MD, Brigham and Women's Hospital, Boston. From Johannsen EC, Sifri CD, Madoff LC. Pyogenic liver abscesses.* Infect Dis Clin North Am. *2000;14:547–563, vii.)*

is successful in 69% to 90% of cases; the procedure is generally well tolerated and usually can be performed at the time of radiographic diagnosis.[60–62,64,147] Aspirated material should be sent for Gram stain and cultured for aerobic and anaerobic bacteria. Meticulous handling of the specimen and rapid transportation to a qualified laboratory are essential for efficient recovery of anaerobes. Histopathologic biopsy specimens should also be obtained if possible. Depending on host and epidemiologic factors, microbiologic evaluation for fungi, mycobacteria, and *E. histolytica* should be considered. The catheter is usually left in place until drainage becomes minimal, typically 5 to 14 days. Recent studies suggest that the success rate for percutaneous drainage with antibiotic treatment is approximately 80% to 95%, even for large (>10 cm) pyogenic liver abscesses.[148–150]

Percutaneous aspiration without catheter placement has received recent attention, with several studies reporting success rates between 58% and 88% for solitary abscesses 5 cm or smaller in diameter, similar to those observed with catheter placement.[61,62,64,151–153] Success rates of 94% to 98% were reported in two studies in which percutaneous aspiration without catheter placement was followed by close clinical monitoring and serial ultrasound studies as indicated. Both investigations found that reaspiration was required in about 50% of cases, and a minority of patients required three or more aspiration procedures.[154,155] Therefore catheter placement may not be required in some patients, but prospective, randomized control trials are necessary to clarify the role of aspiration alone versus catheter placement in the management of hepatic abscess.

Attempts to treat pyogenic liver abscess with antibiotics but no drainage have met with some success. Two early studies with a combined total of 25 patients found cure rates of 87% to 90%.[156,157] These studies have been criticized because 68% of the patients underwent diagnostic aspiration and therefore had at least partial drainage. Moreover, this success rate was substantially higher than the conventional experience at the time, when undrained abscesses carried a mortality rate of 60% to 100%. The results may be subject to selection bias. Most patients did not have drainage because they were deemed poor surgical candidates. Even severely debilitated patients can tolerate percutaneous drainage, but the procedure may not always be required for cure: success rates of 44% and 100% with medical therapy alone have been reported in small case series.[61,149,153,158] Recent studies have also shown that chronic granulomatous disease–associated pyogenic liver abscesses may respond to conservative management with antibiotics and high-dose corticosteroids, delaying and perhaps reducing the future need of percutaneous or open surgical drainage.[159,160] However, until criteria for patient selection are better defined, medical management of pyogenic liver abscess should generally be reserved for patients with small abscesses not amenable to drainage and those patients in whom the risk of drainage is unacceptably high.

Treatment with empirical antibiotics should begin as soon as the diagnosis of pyogenic liver abscess is suspected. Multiple blood cultures should be sent before antibiotic initiation, but delaying antibiotic therapy until abscess material is obtained is not necessary and is potentially dangerous. Antibiotic choice should be guided by the suspected source of the abscess (Table 75.4). Abscesses arising from a biliary source frequently involve enterococci and enteric gram-negative bacilli, whereas abscesses from a colonic or pelvic source are more commonly caused by enteric gram-negative bacilli and anaerobes. Metronidazole at appropriately high doses should be included if amebic liver abscess is a consideration. Fluoroquinolones may be substituted for gentamicin, but this may not be advisable in cases complicated by enterococcal bacteremia. If a hematogenous (hepatic artery) source is suspected, coverage should include an antibiotic with activity against *S. aureus*.

Pyogenic liver abscesses are usually treated parenterally for 2 to 3 weeks, and a 4- to 6-week total course is completed with oral agents. Some have reported successful treatment with less than 2 weeks of antibiotic therapy. The patient's clinical response and follow-up imaging should be monitored to judge response to therapy for considerations of antibiotic duration and the need for further aspiration. One-third of patients are readmitted or have emergency room visits following discharge from the hospital, which suggests that these individuals may benefit from close outpatient follow-up and a multidisciplinary approach to care.[161] Abscess cavities usually resolve completely after therapy, but

TABLE 75.4 Antibiotic Therapy for Pyogenic Hepatic Abscess

TYPE OF THERAPY	AGENTS
Monotherapy	
β-Lactam–β-lactamase inhibitor combination[a]	Piperacillin-tazobactam
Carbapenem[a]	Imipenem-cilastin, meropenem, ertapenem, doripenem
Combination Therapy	
Cephalosporin-based	Third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime) *plus* metronidazole
Fluoroquinolone-based	Fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin) *plus* metronidazole

[a]Metronidazole or tinidazole should be included for presumptive therapy of amebic abscess if suspected.

occasionally they persist despite prolonged courses of antibiotics. In such cases, patients should be observed closely. Recurrent symptoms such as fever or abdominal pain should prompt repeat imaging and possible reaspiration.

INFECTION OF THE BILIARY SYSTEM

Infections of the biliary tract, including the common bile duct and gallbladder, are most often associated with obstruction to the flow of bile. In the United States and many developed countries, gallstones are common and most often asymptomatic. In the United States, for example, it is estimated that 20 to 25 million adults have gallstones.[162] In a small percentage of cases, gallstones may obstruct the cystic or common bile ducts, resulting in inflammation. Approximately 120,000 cholecystectomies are performed every year in the United States for acute cholecystitis, most commonly secondary to impacted gallstones.[163] Other causes of biliary obstruction include tumors of the biliary tree or adjacent structures, strictures secondary to surgery or other injury (including prior infection), and, in many geographic areas, infection by parasites including *Ascaris* and *Clonorchis.* Stasis of bile, inflammation, and loss of mechanical barriers can lead to bacterial infection of the bile, which can result in severe morbidity and death.

Pathogenesis

Cholecystitis

Only about 20% of patients with gallstones experience biliary colic, typified by right upper quadrant pain after a fatty meal when the contracting gallbladder is prevented from emptying by an obstructing stone.[163] Biliary colic must be distinguished from the far more serious acute cholecystitis, which occurs in 1% to 3% of persons with symptomatic gallstones. In this disease, biliary obstruction is accompanied by an intense inflammatory reaction. Obstruction is thought to lead to increased intraluminal pressure; may lead to compromised blood supply and lymphatic drainage; and, in the setting of supersaturated bile, leads to acute inflammation. This process is mediated, at least in part, by prostaglandins, particularly prostaglandins I_2 and E_2 (Fig. 75.2).[164] Infection is not thought to precipitate acute cholecystitis, but it may complicate 20% to 50% of cases. In a microbiologic study of biliary tract processes, 46% of patients presenting with acute cholecystitis had positive bile cultures, compared to 22% of patients with symptomatic gallstones but no evidence of acute cholecystitis and no positive cultures in normal controls.[165] Untreated cholecystitis may resolve spontaneously, but serious complications also occur at a high rate. Once infection is established, complications include gangrenous cholecystitis, emphysematous cholecystitis, gallbladder empyema, pyogenic liver abscess (discussed earlier), and bacteremia.

Acalculous Cholecystitis

In 2% to 15% of cases, cholecystitis occurs in the absence of gallstones, although usually in the presence of other predisposing conditions. These include critical illnesses such as trauma, burns, and sepsis, as well as human immunodeficiency virus (HIV) infection, immunosuppression, diabetes, nonbiliary surgery, and childbirth.[166] Some of these conditions predispose to ischemia in the gallbladder wall or stasis of bile, or both, resulting in concentration of bile salts and leading to inflammation and necrosis of the gallbladder wall.

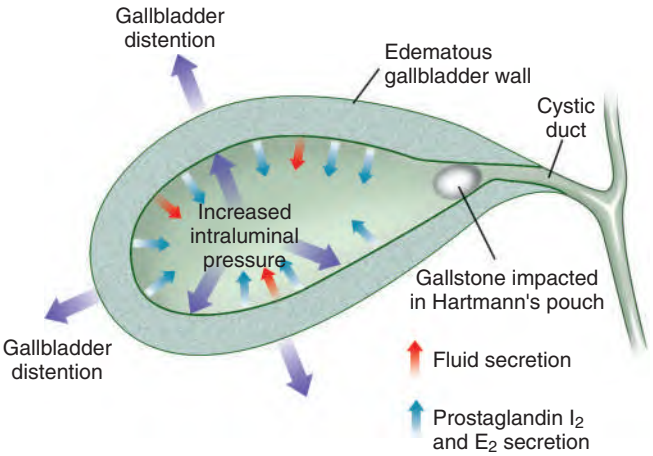

FIG. 75.2 Pathogenesis of acute cholecystitis. Impaction of a gallstone leads to obstruction of the cystic duct and increased intraluminal pressure. An acute inflammatory response is in part mediated by prostaglandins. Infection may then result from biliary stasis. *(Modified from Indar AA, Beckingham IJ. Acute cholecystitis.* BMJ. *2002;325:639–643.)*

Cholangitis

Cholangitis refers to inflammation or infection of the common bile duct. The normally sterile bile may become infected because of the loss of protective factors, including the flow of bile. Obstruction of the common bile duct leads to stasis, which favors the growth of bacteria; increased pressure predisposes to bacteremia. Other factors may involve the loss of antibacterial activity of bile on the proximal small intestine, allowing for greater growth of bacteria. Bacteria may then ascend to the biliary tract (hence the terms *ascending* and *suppurative* cholangitis). Other routes of infection have been proposed, including via the portal system or the lymphatics. Anastomosis of the bile duct to the small intestine, such as in a Whipple procedure, can lead to cholangitis. Primary sclerosing cholangitis is a disease of immunologic origin and is not covered here.[167] AIDS cholangiopathy, which has many features of acute cholangitis, is discussed later in this chapter.

Clinical Manifestations

Patients with biliary tract disease most often present with pain in the right upper quadrant of the abdomen, although occasionally localizing findings are absent. The pain may radiate to the infrascapular region. Cholecystitis and cholangitis are distinguished from simple biliary colic by the continuous nature of the pain. The finding of tenderness in the right upper quadrant on physical examination and the presence of the Murphy sign (inhibition of inspiration by pain when the area of the gallbladder fossa is palpated), with or without a mass, are highly suggestive of biliary tract disease. Fever and tachycardia are frequent findings. Complications of acute cholecystitis, which occur in 10% to 15% of cases, include hepatic or intraabdominal abscess, necrosis or gangrene of the gallbladder, and perforation, which in turn lead to sepsis and peritonitis. Emphysematous cholecystitis, usually diagnosed radiologically, occurs when the wall of the gallbladder is infected with gas-forming organisms, including *Clostridia,* as well as aerobic and facultative gram-negative and gram-positive bacteria. It often occurs in diabetics, and it may suggest a more ominous prognosis.[168,169]

Acalculous cholecystitis, particularly in a critically ill patient who is unresponsive, may produce subtle findings, such as unexplained fever or vague abdominal pain.[170] A high index of suspicion is required because serious complications such as gangrenous gallbladder and perforation frequently occur.

Acute or ascending cholangitis is suggested by the Charcot triad (right upper quadrant or epigastric abdominal pain; fever or chills, or both; and jaundice), reported in 50% to 70% of patients.[171] The additional, less frequent signs of hypotension and altered mental status, in combination with the Charcot triad, constitute the Reynolds pentad, which is reportedly seen in less than 14% of patients with ascending cholangitis.[172] Symptoms and signs of an inflammatory response are usually present and are reflected in the presence of fever, leukocytosis, and other markers.

Diagnosis

Leukocytosis with a left shift is the most frequent laboratory abnormality in acute cholecystitis. Alkaline phosphatase and bilirubin are not usually elevated unless the common bile duct is involved. However, in one study of 217 patients with acute cholecystitis, 25% of patients without obstruction of the common bile duct had elevated bilirubin.[173] Several also had elevations in amylase. The mechanism underlying these abnormalities is unclear but may be the passage of small stones or sludge through the common bile duct. The role of bile and blood cultures in the diagnosis of acute cholecystitis is not well established. International consensus practice guidelines (the "Tokyo Guidelines") recommend obtaining bile and, when available, tissue cultures from patients with cholangitis or moderate-to-severe acute cholecystitis.[174] The utility of routine blood cultures in cases of mild cholecystitis is less clear and are not routinely recommended.[174] Similarly, guidelines of the Surgical Infection Society and the Infectious Diseases Society of America recommend against routinely collecting blood cultures from patients with community-acquired intraabdominal infections, unless the patient is immunocompromised or systemically toxic.[175]

Acute cholangitis results in presentation with the clinical findings mentioned earlier. Abnormalities suggestive of sepsis syndrome, including leukocytosis, are frequently observed. Additional laboratory abnormalities include cholestatic liver function tests with elevations in alkaline phosphatase and bilirubin, particularly conjugated bilirubin. Elevations in γ-glutamyl transpeptidase are often seen as well. Abnormal amylase may suggest an associated pancreatitis, and elevations in transaminases may indicate associated inflammation or infection of the liver parenchyma, or both. The Tokyo guidelines recommend obtaining aerobic and anaerobic cultures of bile aspirates and blood in cases of acute cholangitis.[174] Bile cultures are positive in 59% to 93% of patients, and blood cultures are positive in 30% to 40%.[174,176]

Imaging Studies

Ultrasonography can frequently establish the diagnosis of cholecystitis and is usually the first study obtained.[175] A sonographic Murphy sign (i.e., pain when the ultrasound transducer probes the gallbladder) is a useful diagnostic clue. In addition, the testing may be done at the bedside of critically ill patients, is relatively inexpensive, and can directly visualize stones, particularly in the gallbladder. Abnormalities such as gallbladder wall thickening of greater than 4 mm, pericholecystic fluid, and intramural gas or ductal dilation are suggestive of cholecystitis (Fig. 75.3).[163] The combination of stones and either wall thickening or a sonographic Murphy sign in the appropriate clinical picture were shown to have positive and negative predictive values exceeding 90%.[177]

Radionuclide cholescintigraphy (hepatobiliary iminodiacetic acid [HIDA] scanning) may be used if ultrasound fails to ascertain a diagnosis. A technetium 99m (^{99m}Tc)–labeled derivative of acetanilide iminodiacetic acid is injected intravenously and is secreted into the bile. It is taken up by the gallbladder, which can then be visualized. Failure of the gallbladder to accumulate the marker is highly suggestive of acute cholecystitis due to obstruction of the cystic duct. Normally, visualization of the common bile duct and small bowel occurs within 30 to 60 minutes; failure to visualize these structures indicates obstruction within the common bile duct or at the ampulla. In one study of cholescintigraphy in the diagnosis of acalculous cholecystitis in 62 critically ill patients, ultrasonography had a sensitivity of only 30%, whereas HIDA scanning had a sensitivity of 100% and a specificity of 88%.[178]

CT is not commonly used for the initial evaluation of cholecystitis, and its sensitivity and specificity for detection of this condition are not known.[179,180] CT findings associated with acute cholecystitis include gallstones, particularly within the cystic duct; gallbladder distention and mural thickening; and enhancement of the liver adjacent to the gallbladder, which is the CT equivalent of the scintigraphic "rim sign."

Magnetic resonance (MR) cholangiography is a noninvasive technique that has been used to visualize the bile ducts. In one study of 35 patients comparing ultrasonography with MR cholangiography, the latter modality showed 100% sensitivity for the presence of stones but was less sensitive than ultrasound in the detection of gallbladder wall thickening (69% vs. 96%).[181] In a meta-analysis of 67 studies of MR cholangiography, the technique was highly sensitive (99%) for the detection of biliary obstruction and 92% sensitive for the detection of stones.[182] A more recent meta-analysis of 57 studies found the highest sensitivity (96%) with radionuclide cholescintigraphy, while ultrasonography had a sensitivity of 81%, and MRI had a sensitivity of 85%.[183] The study showed no important differences in specificity among the techniques.

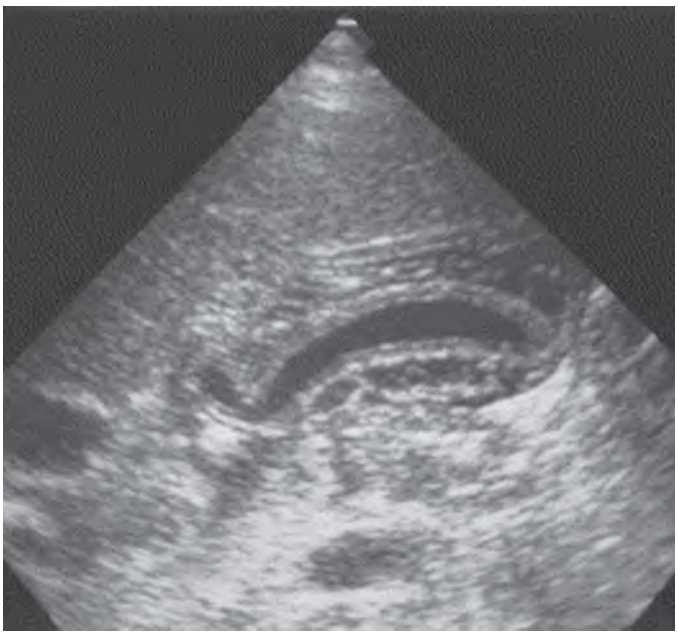

FIG. 75.3 Pathogenesis of acalculous cholecystitis. Ultrasonographic visualization of the gallbladder (sagittal view) in a case of acalculous cholecystitis, demonstrating mural thickening and hypoechoic regions within the gallbladder wall. *(From Gore RM, Yaghmai V, Newmark GM, et al. Imaging benign and malignant disease of the gallbladder.* Radiol Clin North Am. *2002;40:1307–1323, vi.)*

TABLE 75.5 Microbiology of Acute Cholecystitis and Cholangitis

BACTERIA	FREQUENCY (%)
Gram-negative organisms	
Escherichia coli	31–44
Klebsiella spp.	9–20
Pseudomonas aeruginosa	0.5–19
Enterobacter spp.	5–9
Gram-positive organisms	
Enterococcus spp.	3–34
Streptococcus spp.	2–10
Staphylococcus aureus	0–4
Anaerobes	4–20

Modified from Gomi H, Solomkin JS, Schlossberg D, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. *2018;25:3–16.*

Microbiology

Bacterial cultures from the bile and surgical sites of patients with acute cholecystitis and acute cholangitis typically yield constituents of the normal intestinal microbiota (Table 75.5).[174,184] These include gram-negative bacilli such as *E. coli, Klebsiella* spp., and *Enterobacter* spp.

TABLE 75.6 Recommended Agents and Regimens for Empirical Treatment of Acute Biliary Infections

TYPE OF INFECTION	FOR MILD TO MODERATELY SEVERE INFECTION	FOR HIGHLY SEVERE INFECTION
Community-acquired acute cholecystitis	Cephalosporin-based therapy (cefazolin,[a] cefuroxime,[a] or ceftriaxone)	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, or cefepime *plus* metronidazole
Acute cholangitis following biliary-enteric anastomosis	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, cefepime *plus* metronidazole, ciprofloxacin[b] *plus* metronidazole, levofloxacin[b] *plus* metronidazole, or moxifloxacin[b]	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, or cefepime *plus* metronidazole
Health care–associated biliary infection	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, cefepime *plus* metronidazole, ciprofloxacin[b] *plus* metronidazole, levofloxacin[b] *plus* metronidazole, or moxifloxacin[b] Vancomycin[c] added to each regimen	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, or cefepime *plus* metronidazole Vancomycin[c] added to each regimen

[a]Local antimicrobial susceptibility profiles and, if available, isolate susceptibility should be reviewed.
[b]Addition of metronidazole is necessary due to increasing resistance of *Bacteroides* to fluoroquinolones other than moxifloxacin. Local antimicrobial susceptibility profiles and, if available, isolate susceptibility should be reviewed due to increasing resistance of *Escherichia coli* to fluoroquinolones.
[c]Linezolid or daptomycin may be considered in cases where vancomycin-resistant *Enterococcus* (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if VRE is common in the community.
Modified from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. *2010;50:133–164; and Gomi H, Solomkin JS, Schlossberg D, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis.* J Hepatobiliary Pancreat Sci. *2018;25:3–16.*

Anaerobes, most frequently *Bacteroides* spp., *Fusobacterium* spp., and clostridia, are recovered less frequently but are isolated more often from patients with prior biliary tract surgical procedures and those with biliary-intestinal anastomoses. Finally, enterococci are not uncommonly found in infected bile, usually in association with other organisms.[185]

Parasites that infect the biliary tree include *Clonorchis sinensis, Opisthorchis felineus, Opisthorchis viverrini,* and *Fasciola hepatica.*[186] These organisms are prevalent in regions of Asia and can cause acute and relapsing cholangitis with associated stricture and stone formation. *Clonorchis* and *Opisthorchis* infection can lead to the development of carcinoma of the biliary tract. *Ascaris lumbricoides,* a more cosmopolitan parasite, occasionally obstructs the biliary tree, resulting in acute cholangitis.[187] Echinococcal disease can cause biliary obstruction due to mass effect. Parasites that complicate HIV disease may also invade the biliary tree (see discussion following).

AIDS Cholangiopathy (AIDS-Related Sclerosing Cholangitis)

Biliary tract disease is a complication of advanced HIV infection[188] (discussed in Chapter 125). In the era of potent antiretroviral therapy, AIDS cholangiopathy is now a rare clinical entity.[189] Although it is possible that this condition is caused by infection of the biliary tract with HIV per se, more likely it results from opportunistic infection of the biliary system. The pathologic findings of AIDS cholangiopathy include stenosis of the distal common bile duct and irregularities of the intrahepatic and extrahepatic bile ducts.[190] The most common pathogen associated with cholangitis in HIV is *Cryptosporidium.* After an outbreak of cryptosporidiosis in Milwaukee, Wisconsin, in 1995, 29% of patients with HIV infection and intestinal cryptosporidiosis developed cholangiopathy as well.[191] Cytomegalovirus is also a major cause of AIDS-related cholangitis, having been described in up to 42% of patients. Other pathogens associated with AIDS cholangiopathy include *Enterocytozoon bieneusi, Cystoisospora belli,* and *Mycobacterium avium-intracellulare.* The clinical manifestations of biliary tract disease do not differ markedly from those in non–HIV-infected individuals and include right upper quadrant pain and fever. Diagnosis is usually made by characteristic findings on ultrasound, with dilatation of the common bile duct observed in approximately two-thirds of cases. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrates dilatation and irregularities of the ducts and has become the gold standard for the diagnosis.[192] It is also useful in treatment; sphincterotomy provides symptomatic benefit for many patients.

Therapy

Because biliary disease results most commonly from obstruction of the bile ducts, definitive treatment involves removal of the obstruction or the infected material. This can be accomplished surgically, percutaneously, or endoscopically (i.e., by ERCP).[163] Antibiotics and other supportive measures are considered temporizing.

Acute Cholecystitis

The role of antibiotics in acute cholecystitis has not been well established. Many cases of acute cholecystitis remit spontaneously, and retrospective studies of patients with uncomplicated cholecystitis have failed to demonstrate reduced complications such as pericolic abscess or perforation with antibiotic administration.[193,194] In addition, two recent prospective, randomized controlled trials of patients with mild-to-moderate acute cholecystitis managed with early cholecystectomy demonstrated no increase in complications when postoperative antibiotics were withheld, but neither study reached the primary end point of noninferiority.[195,196] Similarly, a recent review of published studies concluded that there was no clear indication that antibiotics are beneficial for patients with acute cholecystitis who were treated conservatively or with delayed cholecystectomy, although the level of evidence was low.[197] In summary, the data suggest that antibiotics can be safely discontinued within 24 hours after cholecystectomy for acute uncomplicated cholecystitis, as long as there is no evidence of infection outside the gallbladder wall.[193]

Antibiotics are clearly indicated for patients with complications of cholecystitis, such as gangrenous cholecystitis or perforation. Guidelines recommend a total of 4 to 7 days of therapy once source control is obtained and anatomic issues have been addressed, although longer courses of treatment may be necessary for complications such as pyogenic liver abscess.[174,175] Antibiotics directed against the enteric flora (as described earlier) should also be given to patients who are debilitated, severely ill, elderly, immunocompromised, or jaundiced (Table 75.6).[174,175] Despite the relatively frequent isolation of enterococci from bile cultures, successful treatment of community-acquired cholecystitis typically does not require antimicrobial therapy against enterococci.[174,175,185] This finding may be a result of the low pathogenic potential of enterococci in this setting; elimination of other pathogens effectively treats the infection even in the setting of persistent enterococcal contamination. However, enterococci may be important pathogens in high-risk patients, such as liver transplant recipients; in these cases, treatment that also targets enterococci may be indicated.[174,175] Institutional drug resistance patterns should be considered when selecting an initial antimicrobial regimen for health care–associated severe cholecystitis. Use of an agent active against gram-negative anaerobes, such as metronidazole, is not required for community-acquired cholecystitis, unless a biliary-enteric anastomosis is present.[174,175]

In the presence of suspected gangrene or perforation, immediate surgery is indicated. Ideally, this includes cholecystectomy with intraoperative cholangiogram. Alternatively, in unstable patients, cholecystotomy (percutaneous drainage of the biliary system with removal of obstructing stones) may be performed as a temporizing measure.[198] This procedure can be performed under local anesthesia and at the bedside in critically ill patients and can be lifesaving. In some circumstances, further surgery may not be required.

In the absence of severe complications, the timing of definitive surgical intervention in the management of acute cholecystitis is the subject of

some debate. Traditionally, in the group of patients who are stable and respond to conservative management, surgery has been delayed for 6 to 12 weeks. However, several studies have shown that patients who undergo early surgical intervention (most often laparoscopic cholecystectomy) have a lower complication rate, a shorter hospital stay, and, if laparoscopic cholecystectomy is performed, a lower requirement for conversion to an open procedure, compared with patients undergoing delayed surgery.[199,200] Several recent meta-analyses of randomized controlled trials found early surgery to be as safe and effective as delayed surgery and associated with lower hospital costs, fewer work days lost, and lower risk of wound infection.[201–203] For patients with high surgical risk and those who are unstable, delayed surgery may still be preferable.

Acute Cholangitis

Acute cholangitis remains a disease with substantial mortality, and therapy should include antibiotics and supportive measures along with decompression/drainage of the biliary system for cases that do not respond promptly to conservative therapy. A variety of antibiotic regimens have been used in the management of acute cholangitis (see Table 75.6).[172,174,175] Empirical coverage should be directed against enteric gram-negative bacilli. A β-lactam–β-lactamase inhibitor such as piperacillin-tazobactam is appropriate initial empirical therapy.[174] Cephalosporins, carbapenems, and fluoroquinolones have also proved efficacious.[172,174,176] Selection of empirical antibiotic therapy in cases of health care–associated disease should be influenced by local nosocomial resistance patterns, as well as the patient's prior antibiotic exposures and known microbial colonization.[174,175] Although anaerobes are only infrequently cultured from bile in acute cholangitis, the addition of metronidazole to empirical third- or fourth-generation cephalosporin-based regimens is advisable (see Table 75.6).[174,175] Like severe acute cholecystitis, acute cholangitis is treated for a total of 4 to 7 days once source control is obtained and anatomic problems have resolved, although longer courses of treatment may be necessary due to complications such as pyogenic liver abscess or gram-positive bacteremia.[174]

Drainage of the biliary tract may be accomplished surgically, endoscopically, or percutaneously. ERCP has, to a large extent, supplanted open surgical procedures in the management of acute cholangitis and is successful in more than 90% of cases.[204,205] (Paradoxically, ERCP is not infrequently the cause of acute cholangitis when it is used in an attempt to decompress an obstructed but not frankly infected bile duct.[206]) ERCP is generally thought to have a lower morbidity rate than open surgery, and it is more likely to offer definitive treatment (e.g., by removal of an impacted gallstone) than percutaneous biliary drainage. Some cases of acute cholangitis will respond to conservative therapy with drainage deferred until 24 to 48 hours to monitor response.[207,208]

Treatment of parasitic infections affecting the biliary tree is covered in Chapters 287, 289, and 290.

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76 Pancreatic Infection

Miriam Baron Barshak

SHORT VIEW SUMMARY

Definition
- Infection of pancreatic tissue.
- Most commonly develops as a complication of acute pancreatitis (AP), in tissue that has been damaged by inflammation (see Table 76.2).
- Pancreatic abscess is a circumscribed collection of pus usually in or near the pancreas, arising as a consequence of AP or pancreatic trauma.

Epidemiology
- Approximately 275,000 admissions for AP per year in the United States, up to 20% of which may have significant pancreatic necrosis.
- Up to 70% of patients with pancreatic necrosis may develop pancreatic infection.

Microbiology
- Gastrointestinal bacterial microbiota most common (aerobes and anaerobes, gram-positive, and gram-negative).
- Use of preemptive antibiotics may select for more resistant bacterial species and fungal pathogens.

Diagnosis
- Must be distinguished from sterile pancreatic necrosis, which can be associated with a sepsis-like syndrome.
- Tissue sampling may be required to identify infection.

Therapy
- Antimicrobial therapy targeting organisms identified in cultures of the infected site, in combination with catheter drainage and/or surgical removal of the infected material (see Table 76.3).
- Delay in surgery for infected pancreatic necrosis until it has evolved to walled-off necrosis may allow a more stable patient with better-demarcated areas of necrotic tissue and is now the favored approach.
- Newer surgical approaches include video-assisted retroperitoneal débridement and endoscopic transgastric necrosectomy.

Prevention
- Enteral nutrition rather than parenteral nutrition, starting as soon as possible (within 72 hours of admission for patients with severe AP); nasogastric or nasojejunal tubes are equivalent.
- A consensus favoring use of early (preemptive) systemic antibiotics emerged in the 1990s and 2000s, using carbapenem alone or quinolone plus metronidazole as first-choice therapy.
- More recent randomized controlled studies have not demonstrated a benefit from this practice, and most guidelines advise *against* the use of preemptive antibiotics for patients with AP.

Inflammation of pancreatic tissue commonly manifests as severe acute upper abdominal pain and elevated serum levels of pancreatic enzymes. Most episodes of acute pancreatitis (AP) are associated with gallstones or alcohol abuse. Other causes of AP are hypercalcemia, hypertriglyceridemia, anatomic abnormalities, familial syndromes, autoimmune disease, ischemia, pancreatic carcinoma, trauma, endoscopic retrograde cholangiopancreatography, and drugs, among which are antimicrobial agents such as tetracycline, pentamidine, sulfonamides, didanosine, erythromycin, nitrofurantoin, and metronidazole.[1,2] Infection of damaged pancreatic tissue may complicate disease initiated by any of these mechanisms, conferring significant morbidity and mortality risks. Less commonly, many different microorganisms may infect the pancreas directly, with or without inciting a syndrome of AP. This chapter reviews the infectious agents associated with primary pancreatic infection before focusing on infectious complications of AP. Issues of nonpancreatic infection related to gallstones are addressed in Chapter 75.

INFECTIOUS CAUSES OF ACUTE PANCREATITIS

Many organisms have been reported to cause pancreatic disease. Case reports in this area have been reviewed and assessed for adequate documentation of both pancreatitis and infection (Table 76.1).[3] The reports of "definite" or "probable" association with pancreatitis described patients with coxsackieviruses, cytomegalovirus (CMV), varicella-zoster virus, herpes simplex virus 2 (HSV-2), mumps virus, hepatitis B virus, and with infections caused by *Mycoplasma, Leptospira, Legionella, Salmonella enterica* serotype Typhi, *Aspergillus, Toxoplasma, Cryptosporidium*, and *Ascaris*.

Among these, ascariasis commonly causes pancreatic-biliary disease in countries with high infection rates; in some tropical areas, ascariasis ranks second to gallstones as a cause of pancreatitis.[4] After hatching in the duodenum, *Ascaris* larvae penetrate the small bowel mucosa, enter the venous circulation, and arrive in the lungs, where they enter the alveolae, ascend the bronchial tree, and are swallowed. In the gastrointestinal (GI) tract they mature into adult worms and then may cause clinical and pathologic AP by migrating across the ampulla of Vater to obstruct the common bile duct or the pancreatic duct.

Other organisms, including Epstein-Barr virus, vaccinia, rubella, adenovirus, and rubeola, have been cited as causes of pancreatic infection in case reports but without adequately rigorous investigation to qualify for definite or probable association with pancreatitis.[3]

Another group of organisms causes pancreatic infection, forming microabscesses or macroabscesses but without inducing the signs, symptoms, or pathology of AP (see Table 76.1).[3]

Thus pathologic or radiographic evidence of pancreatitis associated with well-documented infection has been noted with viruses, bacteria, fungi, and parasites. However, the frequency with which these organisms contribute to idiopathic pancreatitis is unclear.

PANCREATITIS AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Although human immunodeficiency virus (HIV) itself has not been identified in pancreatic tissue by molecular methods, HIV infection has been associated with an increased risk of clinical pancreatitis. One study reports a 14% incidence of mild-to-moderately severe AP among patients with HIV between 1993 and 1994, with an inverse correlation between serum pancreatic enzyme level and number of CD4 lymphocytes.[5] Etiologies of pancreatitis frequently seen in HIV-infected patients include drugs (e.g., pentamidine, didanosine, and

TABLE 76.1 Infectious Causes of Pancreatic Disease

Definite[a] or Probable[b] Pancreatitis
Ascaris
Aspergillus
Coxsackievirus B, B3, B4
Cryptosporidium
Cytomegalovirus
Hepatitis B virus
Herpes simplex virus 2
Legionella
Leptospira
Mumps virus
Mycoplasma
Salmonella Typhi
Toxoplasma
Varicella-zoster virus
Probable Pancreatic Infection[c] Without Acute Pancreatitis
Actinomyces
Candida spp.
Clonorchis sinensis
Coccidioides immitis
Cryptococcus neoformans
Echinococcus granulosus
Entamoeba histolytica
Histoplasma capsulatum
Leishmania donovani
Mucormycosis
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis
Nocardia asteroides
Paracoccidioides brasiliensis
Paragonimus westermani
Pneumocystis jirovecii
Schistosoma haematobium
Strongyloides stercoralis

[a]Pancreatitis at surgery or autopsy, or radiographic evidence.
[b]Threefold increase in amylase and/or lipase as well as characteristic symptoms.
[c]Culture of the organism from blood or pancreatic juice, or serologic diagnosis in a characteristic clinical or epidemiologic setting.
From Parenti DM, Steinberg W, Kang P. Infectious causes of acute pancreatitis. Pancreas. *1996;13:356–371.*

trimethoprim-sulfamethoxazole) and opportunistic infections (e.g., CMV, HSV, and others listed earlier). For the most part, however, the infections (microabscesses or macroabscesses) in these reports were noted incidentally at autopsy, without prior associated symptoms or pathologic evidence of AP. In addition, advanced HIV infection is associated with an increased risk of pancreatic malignancies, including Kaposi sarcoma and lymphoma, which may lead to signs, symptoms, or laboratory abnormalities suggesting pancreatitis. Finally, isolated pancreatic enzyme elevations have been noted in HIV-infected patients lacking other signs or symptoms of pancreatitis.[6] In the study discussed earlier[5] the most frequent causes of pancreatitis were gallstones, alcohol or intravenous (IV) drug abuse, pentamidine intake, and infections with *Pneumocystis jirovecii* and *Mycobacterium avium-intracellulare* complex. Of note, no pancreatic tissue sampling was performed to document the presence of these microorganisms.

INFECTION COMPLICATING ACUTE PANCREATITIS

Background

Most pancreatic infections occur as complications of AP initiated by noninfectious causes. Regardless of the inciting event, the pathogenesis of AP involves activation and release of toxic materials, including pancreatic proteolytic enzymes and vasoactive substances (trypsin, cathepsin B, phospholipase, chymotrypsin, elastase, cytokines, and the kallikrein-kinin, coagulation, and fibrinolysis cascades) that injure pancreatic cells and blood vessels. Such damage increases vascular permeability and leads to pancreatic swelling, a condition described clinically as interstitial edematous pancreatitis. Accounting for 80% of AP cases,[7] this disorder usually responds well to supportive care. In more severe disease, liberation of these toxic materials into the surrounding retroperitoneal spaces, lesser sac, and peritoneal cavity causes chemical irritation and contributes to third-space losses of protein-rich fluid, leading to hypovolemia and hypotension. In 5% to 15% of AP cases, hypoxia, free radicals, and ongoing release of pancreatic enzymes cause disruption of the pancreatic microcirculation, which leads to more severe pancreatic tissue injury and ultimately pancreatic necrosis. In addition, recruited inflammatory cells release substances such as phospholipase A_2, polymorphonuclear cell elastase, interleukins, leukotrienes, and complement factors, which contribute to a systemic inflammatory response syndrome (SIRS) that may include fever, acute respiratory distress syndrome, pleural effusions, renal failure, shock, myocardial depression, and metabolic abnormalities.[8] Necrotizing pancreatitis is associated with mortality rates of 30% to 40%.[9] Twenty percent of the deaths occur during the first week of illness in the setting of this inflammatory milieu and associated multiple organ failure. Later deaths from AP often occur in association with local and systemic infectious complications.[10] Predisposition to infection in severe AP may be related in part to altered immune responses; in one report, aberrant monocyte signaling profiles were identified that could alter immune defenses, including monocyte transmigration.[11]

Significance of Infection in Acute Pancreatitis

Some reports suggest that infection increases mortality rates. In one series of 114 patients with pancreatic necrosis, intestinal microorganisms were cultured from the necrotic tissue in 39.4% of cases. Mortality rates in patients with less than 50% gland necrosis rose from 12.9% to 38.9% if the necrotic tissue was infected, whereas mortality rates in patients with greater than 50% necrosis rose from 14.3% to 66.7% in the presence of infection.[12] Of note, other studies have reported that the mortality rates among patients with severe sterile necrosis are equal to those among patients with infected necrosis.[13] Nonetheless, the association of mortality with infection in AP in some studies suggests that preventing, identifying, and treating infections might decrease the risks of adverse outcomes. A 2010 meta-analysis further supports this idea with the finding that among nearly 1500 patients with AP, the absolute influence of organ failure and infected pancreatic necrosis on mortality is comparable, and thus the presence of either indicates severe disease—that is, the relative risk (RR) of mortality doubles when organ failure and infected pancreatic necrosis are both present and indicates extremely severe disease or critical AP.[14] A 2014 prospective study found organ failure to have more effect on mortality than infection among patients with necrotizing pancreatitis but confirmed that each was a significant, independent predictor of death in a multivariate analysis.[15]

Although infection is rare in mild pancreatitis, severe pancreatitis is associated with infection rates as high as 70%.[12,16–19] This difference in infection risk has driven extensive efforts to identify patients with severe pancreatitis early in the course of illness. Multiple criteria have been suggested, with some agreement that severe AP is characterized by abnormalities in physiology (an Acute Physiology and Chronic Health Evaluation [APACHE II] score <8 or equivalent for other scoring systems), in conjunction with computed tomography (CT) evidence of less than 30% pancreatic necrosis, chest radiographic evidence of pleural effusions, and C-reactive peptide (CRP) value less than 150 mg/L.[20] Of importance, the risk of infection increases with the extent of necrosis.[12,21]

Defining Pancreatic Infections

Pancreatic collection nomenclature, derived by consensus at the International Symposium on Acute Pancreatitis in Atlanta in 1992,[22] and revised in 2012,[23] is summarized in Table 76.2. In early AP[13] local infection may arise in necrotic pancreatic and peripancreatic tissue without significant pus collections.[24] The incidence of infection increases with the extent of necrosis and with time.[25] In one study 49% of infections in necrotizing pancreatitis developed within the first 2 weeks of illness, whereas 71% of infections developed within the first 3 weeks of illness.[13] Another group reported the incidence of infection was highest among patients undergoing surgery 15 to 21 days into illness.[12] The contamination rate was 24% within the first week after onset of symptoms and then rose to 36% and 71% within 2 and 3 weeks, respectively.

TABLE 76.2 Definitions Derived From the International Symposium on Acute Pancreatitis, 1992 and Revised in 2012

TERM	DEFINITION
Acute pancreatitis	Acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems
Necrotizing pancreatitis	Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
ANC (acute necrotic collection)	A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
APFC (acute peripancreatic fluid collection)	Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis; term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial edematous pancreatitis and without the features of a pseudocyst
Pancreatic pseudocyst	An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis; entity usually occurs >4 weeks after onset of interstitial edematous pancreatitis to mature
WON (walled-off necrosis)	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall; WON usually occurs >4 weeks after onset of necrotizing pancreatitis

From Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. *2013;62:102–111.*

Later in the course of AP (weeks 4–7), after the serum markers of pancreatitis resolve, pancreatic necrosis liquefies into fluid collections; sterile necrosis thus develops into pancreatic pseudocysts, whereas infected necrosis matures into walled-off necrosis (WON) in about 3% of patients with necrotizing pancreatitis.[12,17] Pseudocysts may subsequently become superinfected and develop into abscesses as well. Pancreatic abscess typically is seen with fever, abdominal pain, and leukocytosis in patients recovering from recognized pancreatic disease. In general, more systemic toxicity and mortality occur with infected necrosis than with pancreatic abscess. Specifically, mortality rates of 26% to 32.1% have been reported for infected necrosis versus 12% to 22.2% for abscess.[13,24]

Diagnosis of Pancreatic Infection

Identifying infection in AP can be difficult because patients with extensive necrosis of pancreatic and peripancreatic tissue frequently display a sepsis-like syndrome without a septic focus. Such patients may develop physiologic abnormalities indistinguishable from those associated with infection, including systemic organ failure syndrome involving the lungs, kidneys, liver, and cardiovascular systems. In one study[26] 60% of AP patients developed fever; in 22% the fever was related to pancreatitis per se; in 33% it was attributed to extrapancreatic infections; and in 45% it was due to infected pancreatic necrosis. Imaging by CT can aid in diagnosing infected pancreatic necrosis only if gas is seen in and around areas of pancreatic necrosis. Several laboratory parameters have been evaluated as markers of pancreatic infection; the most promising of these is procalcitonin, a 116–amino-acid propeptide of calcitonin, but more data from larger studies must be obtained.[27,28] A 2007 study addressed the value of routine clinical tests (white blood cell [WBC] and CRP) in predicting the development of infected pancreatic necrosis in severe AP. The authors reported that if CRP and WBC values were below cutoff values (81 mg/L for CRP and 13×10^9/L for WBC), the risk for infected necrosis was approximately 1.4%. The authors suggest that invasive testing to diagnose infection may be unnecessary in this subset of patients.[29] In other patients, however, tissue sampling can be helpful to identify infection; Gram stain and culture of pancreatic tissue sampled by CT-guided fine-needle aspiration (FNA) provides high diagnostic sensitivity and specificity with minimal risk of introducing infection or disseminating organisms by intestinal puncture.[13] This procedure has been recommended for patients with necrotizing AP and persistent systemic toxicity or organ failure, or both, in the first 7 to 14 days. Similarly, culture of material retrieved by FNA of collections, seen by CT or ultrasound imaging, allows diagnosis of extrapancreatic infection. Such collections may spread from the pancreas into the retroperitoneum, mesentery, mediastinum, and elsewhere, through tissue damaged by activated proteases, vasoactive substances, and inflammatory mediators.[30] Positron emission tomography/CT with ^{18}F-fluorodeoxyglucose–labeled leukocytes may be helpful in distinguishing infected from uninfected collections less invasively.[31]

More recently a 2014 Dutch study found that infected necrosis could generally be diagnosed based on clinical or imaging signs of infection with positive predictive value of 80% to 94%, but FNA may be useful in patients with unclear clinical signs and no imaging signs of infected necrosis.[32] However, a 2014 study from Boston found from open necrosectomy that the false-negative rate of percutaneous sampling to assess for infection was 20%. The authors conclude that the decision for débridement therefore should not be predicated on proven infection from a percutaneous sample.[33]

Microbiology of Pancreatic Infection

Pancreatic superinfection usually involves GI microbiota, including aerobes and anaerobes. Historically, both gram-negative (most commonly *Escherichia coli* and *Klebsiella* spp., less commonly *Enterobacter, Pseudomonas, Proteus*, and others) and gram-positive (enterococcal, streptococcal, and staphylococcal species) bacteria contribute, and infections may be monomicrobial or polymicrobial. In a collected series of 45 articles, representing more than 1100 cases of secondary pancreatic infections reported as of 1990,[34] the causative organisms were *E. coli* (35%), *Klebsiella pneumoniae* (24%), *Enterococcus* spp. (24%), *Staphylococcus* spp. (14%), and *Pseudomonas* spp. (11%). A more recent (2014) single-center review noted enterococci (45%), Enterobacteriaceae (42%), and fungi (22%).[35]

One group[36] has reported a different microbiologic picture of infected pancreatic necrosis in alcoholic and biliary pancreatitis among 70 patients with similar degrees of necrosis who underwent surgery for pancreatitis. These authors note a higher rate of infection overall and a preponderance of gram-negative organisms in the biliary disease patients, compared with a tendency toward more gram-positive pancreatic infections in the alcoholic group. The authors hypothesize that these differences might be explained by a biliary origin of pancreatic infection among patients with biliary disease, in contrast to a hematogenous origin of infection from catheter contamination in the alcoholic population. Of note, other work has shown that mortality from pancreatitis is related to the severity of the attack and not the underlying cause.[37]

Earlier exposure to broadly active antimicrobial therapy changes the microbiota that cause infections, and increasingly resistant bacterial infections and fungal infections have become more common.[38] A study of 479 patients with acute pancreatitis, of whom 17 had intraabdominal fungal infections, identified administration of prophylactic antibiotics on admission as a statistically significant risk factor.[39] Fungal infection in AP is associated with a higher incidence of systemic complications and perhaps also mortality. In addition to broad-spectrum antibiotic exposure, additional risk factors for fungal infection include prolonged hospitalization, surgical/endoscopic interventions, use of total parenteral nutrition (TPN), and mechanical ventilation.[40]

Overall, the profile of organisms suggests most pancreatic infections originate in the GI tract and seed the pancreas via the bowel, the biliary tree, the lymphatics, or the bloodstream. Initially, bowel microbiota may translocate across a GI mucosal barrier damaged by ischemia during the hypovolemic phase of AP.

Management of Pancreatic Infection

In most cases treating pancreatic infection requires antimicrobial therapy directed at organisms identified in cultures of the infected site, in combination with mechanical removal of the infected material. Although

some groups[41] have reported successful medical management of infected necrosis, most have traditionally believed that removal of infected necrosis and all associated fluid collections is necessary.

Several studies suggest that infected pancreatic necrosis may be managed successfully via catheter drainage, without surgical intervention. In one report primary CT-guided percutaneous catheter drainage was successful for approximately one-half of the patients with acute necrotizing pancreatitis, and the presence of multisystem organ failure was a more important indicator of outcome than the presence of infection.[42] There is some support for the initial drainage efforts to be made endoscopically (i.e., transluminally) rather than percutaneously, with the possible benefit of preventing development of an external pancreatic fistula that could be promoted by percutaneous drainage.[43]

For patients in whom initial drainage is inadequate, a "step-up" to surgical removal of infected material should be pursued using either minimally invasive approaches (endoscopic, laparoscopic, retroperitoneal, percutaneous) or more traditional surgical approaches (i.e., necrosectomy with continuous closed lavage, débridement with open packing, or necrosectomy and drainage with planned reoperation).[44,45] Surgical management often requires multiple staged operations to remove all necrotic pancreatic and peripancreatic material. A 2014 study from Boston found that open débridement was associated with low in-hospital mortality (8.8%).[33]

The timing of surgical removal is a matter of some debate in the older literature. The intended benefit from early intervention is prompt removal of the infected material in hopes of more rapid resolution of the inflammatory processes. However, newer studies demonstrate a benefit from a delay in surgery that may allow for a more stable patient with better-demarcated areas of necrotic tissue.[46,47] For this reason, practice has evolved toward waiting on surgical intervention until the 4-week point if possible, to allow walling off of the necrotic collection and softening/liquefaction of its contents. There is some experience with local administration of antimicrobials via catheter into areas of necrosis that cannot be removed.[48]

In contrast to infected necrosis, postpancreatitis abscesses remote from the pancreas itself and superinfected pancreatic pseudocysts are unlikely to be associated with significant amounts of necrotic tissue; these may be managed successfully by catheter drainage or by surgical drainage in conjunction with appropriate antimicrobial therapy.[30]

Prevention of Pancreatic Infection

Because infection may be associated with increased mortality rates in AP despite aggressive medical and surgical therapy, major efforts have been oriented toward preventing infection. Studies have focused on maintaining the gut barrier function, probiotics, selective decontamination of the digestive tract (SDD) with oral, nonabsorbable antibiotics, and early therapy with systemic antibiotics. A reasonable aim for such studies is to identify interventions that decrease the frequency of pancreatic infection, leading to fewer surgical procedures and lower mortality rates.

Early Enteral Feeding

Several groups have studied enteral feeding in AP for its ability to lower infection risk both by reducing dependence on central venous access for parenteral alimentation and by sustaining the integrity of the intestinal barrier. In animal studies of AP[49] enteral nutrition was associated with less bacterial and/or endotoxin translocation into mesenteric lymph nodes but did not influence pancreatic healing or overall survival. In one study of humans, 38 patients with severe AP were randomized to parenteral nutrition or to enteral nutrition via nasojejunal tube (NJT) within the first 48 hours after admission. The NJT patients suffered fewer complications ($P < .05$) and fewer infectious complications ($P < .01$).[50] Of note, all patients received imipenem from admission until clinical recovery and restoration of normal CRP concentrations. The authors speculate that enteral feeding "improves the gut immune system, restores normal gut structure and microbiota, and aids the mucosa in withstanding challenges… it is, in fact, still unclear whether enteral feeding improves the rate of septic morbidity or whether TPN itself causes an increase in septic complications." Another study of 89 patients with pancreatitis observed that enteral nutrition significantly reduced septic complications but did not affect the rates of multiple organ failure or death.[51] In a randomized trial of 208 patients with severe pancreatitis, early enteric feeding initiated within 24 hours after randomization was not superior to an oral diet initiated 72 hours after presentation in reducing rates of infection or death.[52]

Probiotics have been evaluated in addition to enteral feeding. A randomized, double-blind study showed significantly less pancreatic sepsis and fewer surgical interventions in 22 AP patients given live *Lactobacillus* for 1 week, compared with 23 control patients given heat-killed *Lactobacillus*. Both groups received early enteral feeding with oat fiber supplementation as a substrate for the lactic acid bacteria.[53] In a subsequent double-blind, placebo-controlled study, 298 patients with severe AP received a multispecies probiotic product or placebo, administered via NJT along with tube feeding. Infection rates were similar between groups, but mortality was higher in the probiotic group (16% vs. 6%; RR, 2.53). Nine patients in the probiotic group developed bowel ischemia (8 of whom died), compared with none in the placebo group ($P = .004$). The researchers concluded that this probiotic should not be administered to patients with predicted severe AP.[54] Commentators provide several possible explanations for these unexpected results, including a potentially harmful interaction between the probiotic and the enteral feeding formula used. They also speculate that "patients with multiorgan dysfunction who need vasopressors to maintain systemic circulation might have severe splanchnic hypoperfusion. Probiotics with enteral feeding might result in intestinal oxygen consumption exceeding supply, resulting in overt ischemia."[55] In a follow-up study, bacteremia, infected necrosis, organ failure, and mortality were all associated with intestinal barrier dysfunction early in the course of AP. This was determined by measuring excretion of intestinal fatty acid binding protein (a parameter for enterocyte damage), recovery of polyethylene glycols (a parameter for intestinal permeability), and excretion of nitric oxide (a parameter for bacterial translocation) in urine samples that were collected 24 to 48 hours after randomization to probiotic or placebo treatment and 7 days thereafter from 141 patients with predicted severe AP. The specific combination of probiotic strains used in this study reduced bacterial translocation overall but was associated with increased bacterial translocation and enterocyte damage in patients with organ failure.[56]

Selective Decontamination of the Digestive Tract

SDD aims to eradicate carriage of potentially pathogenic organisms from the GI tract. Animal studies of SDD, reviewed by Ratschko and coworkers,[7] show a mortality benefit in AP. Of some concern, however, studies in rats suggest that eliminating gram-negative bowel microbiota may facilitate overgrowth of *Enterococcus* spp. in the gut and increase the risk of gram-positive infections from translocation of GI microbiota.[57]

Only one controlled study in human patients evaluated the effects of SDD on infection rates in pancreatitis (Table 76.3).[58] In this trial patients with severe AP, but without pancreatic necrosis on CT, were randomized to receive conventional therapy or conventional therapy plus SDD (enteral colistin, norfloxacin, and amphotericin B). The SDD group also received IV cefotaxime until aerobic gram-negative bacteria were eliminated from the oral cavity and rectum. There was no difference in mortality. However, correcting for illness severity yielded a narrow survival benefit for the SDD group ($P = .048$) that was attributable to a decrease in infected necrosis (18% vs. 38%, $P = .03$), with an effect on gram-negative pancreatic infection in particular (8% vs. 33%, $P = .003$). Of note, sterile pancreatic necrosis was documented in 11 of 16 patients who died within 2 weeks of onset (mostly from multiple organ dysfunction syndrome), suggesting that mortality was unrelated to infection. The administration of IV cefotaxime along with SDD in this study obscures interpretation of the effect of SDD alone.

In a follow-up report[59] the authors of this trial noted that among patients in both the SDD and control groups, gram-negative infection of pancreatic necrosis was associated with a mortality rate 15-fold higher than that associated with sterile necrosis, whereas gram-positive pancreatic infection was not associated with an increase in mortality rate. Of interest, there was no significant difference in the incidence of

TABLE 76.3 Pancreatic Infection Incidence and Mortality Rate in Controlled Trials with Antibiotics and Meta-analyses

AUTHOR	ANTIBIOTIC	NO. OF PATIENTS	PANCREATIC INFECTION RATE (%) CONTROL/CASE	MORTALITY RATE (%) CONTROL/CASE	COMMENTS
Luiten et al.[58]	SDD: enteral colistin, norfloxacin, and amphotericin B, until clinical recovery plus IV cefotaxime until gram-negative bacteria are eliminated from the oral cavity	102 severe AP	38/18[a]	35/22	Nonblinded. Necrosis not defined. Mortality difference statistically significant when disease severity differences between the groups are taken into account. Predominant effect on gram-negative pancreatic infection (8% in SDD group vs. 33% in conventional treatment group). Treatment with IV cefuroxime as well as enteral SDD obscures interpretation of the effect of enteral treatments alone
Pederzoli et al.[21]	Imipenem, 500 mg IV tid, 14 days	74 necrotizing pancreatitis, mostly of biliary origin	30/12[a]	12/7	Not placebo-controlled. Nonpancreatic infections also reduced (15% vs. 49%, $P < .01$). No change in multiorgan failure rate, need for surgery, or survival compared with no early antibiotic treatment
Sainio et al.[66]	Cefuroxime, 1.5 g IV tid, until clinical recovery and normalization of CRP level	60 severe acute alcoholic pancreatitis and necrosis of at least one-third of the pancreas by contrast-enhanced CT	40/30	23/3[a]	Not placebo-controlled. Reduction in total infections, infections per patient, and operations also statistically significant. Rate of culture-proven sepsis not statistically significant. Only urinary tract infections were reduced significantly
Delcenserie et al.[67]	Ceftazidime, amikacin, and metronidazole IV, 10 days	23 alcohol-induced severe AP	58/0[a]	25/9	CT with two or more fluid collections, necrosis not defined
Schwarz et al.[68]	Ofloxacin and metronidazole IV, 10 days	26 CT-confirmed pancreatic necrosis	53/61	15/0	Not placebo-controlled. FNA performed on days 1, 3, 5, 7, and 10 in all patients; antibiotics given to control patients with evidence of infection. Better clinical course in intervention group, but no effect on development of pancreatic infections
Bassi et al.[38]	Pefloxacin (400 mg bid) vs. imipenem (500 mg tid), 14 days	60 severe necrotizing pancreatitis	Pefloxacin: 33[a] Imipenem: 10[a]	Pefloxacin: 24 Imipenem: 10	Nonblinded. CT confirmed at least 50% necrosis
Isenmann et al.[72]	Ciprofloxacin (400 mg bid) and metronidazole (500 mg bid) IV, *or* placebo, 14 or 21 days	114 AP plus serum CRP >150 mg/L and/or necrosis on contrast-enhanced CT	12/9	5/7	Randomized, double-blinded, placebo-controlled; 28% of CIP/MET group and 46% of placebo group required open antibiotic treatment; most placebo group switches motivated by extrapancreatic infections; overall mortality and rates of pancreatic infection low, number of patients with pancreatic necrosis low
Golub et al.[69]	Meta-analysis of eight controlled trials, including trials from the 1970s[21,58,61,101–103]				Findings: Early antibiotic administration reduced mortality from AP but only for patients with severe pancreatitis who received broad-spectrum antibiotics reaching therapeutic levels in pancreatic tissue
Sharma et al.[70]	Meta-analysis including only randomized, controlled, nonblinded studies evaluating patients with necrotizing pancreatitis who received either no preemptive antibiotics or preemptive treatment with antibiotics reaching therapeutic levels in necrotic pancreatic tissue[21,66,67]	84 received antibiotic prophylaxis; 76 did not; of note, the total of 160 patients in the pooled data set is inadequate for detection of a 50% reduction in the rate of infections[60]			Findings: Nonsignificant trend toward decreased local infection in patients given early imipenem, cefuroxime, or ofloxacin. Incidence of sepsis and overall mortality significantly lower (absolute risk reductions, 21.1% and 12.3%, respectively, for a relative risk reduction of 72%) for antibiotic treatment. On this basis, the authors recommend that "all patients with acute necrotizing pancreatitis…be given prophylaxis with an antibiotic with proven efficacy in necrotic pancreatic tissue."