Peritonitis: Update on Pathophysiology, Clinical Manifestations, and Management

Caroline C. Johnson, James Baldessarre, and Matthew E. Levison

Peritonitis results from any local trigger of inflammation. Usually infection is the trigger, although infection may not necessarily be present at the earliest stage. For example, sterile peritonitis may occur in the localized peritoneal space surrounding an infected but resectable intraabdominal organ, such as the appendix or gallbladder. In contrast, there may be contamination of the peritoneum from a defect in the intestinal wall, before establishment of infection or onset of an inflammatory response, e.g., immediately following penetrating abdominal trauma. Peritonitis has been categorized as primary, secondary, or (more recently) tertiary. Peritonitis complicating peritoneal dialysis can be considered as an additional category. Each of these categories is reviewed herein, with an emphasis on recent developments in pathogenesis, evaluation, and management.

Primary Peritonitis

Pathogenesis. Primary peritonitis is an infection of the peritoneal cavity not directly related to other intraabdominal abnormalities. The vast majority of cases are due to bacterial infection; it is also commonly known as spontaneous bacterial peritonitis. Usually it occurs in the presence of ascites from any of a variety of underlying conditions [1]. In the preantibiotic era, primary peritonitis accounted for ~10% of all pediatric abdominal emergencies; it now accounts for <1–2% [2]. 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, it is especially associated with postnecrotic cirrhosis and nephrotic syndrome. In adults, primary peritonitis develops in up to 25% of patients with alcoholic cirrhosis but has also been reported to occur in adults with postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, metastatic malignant disease, systemic lupus erythematosus, and lymphedema and, rarely, in adults with no underlying disease [3]. The presence of ascites appears to be the common link among these various conditions.

The route of infection in primary peritonitis is usually not apparent but is thought to be hematogenous, lymphogenous, via transmural migration through an intact gut wall from the intestinal lumen, or, in women, from the vagina via the fallopian tubes. In cirrhotic patients the hematogenous route is most likely. Organisms removed from circulation by the liver may contaminate hepatic lymph and pass through the permeable lymphatic walls into the ascitic fluid. In addition, portosystemic shunting greatly diminishes hepatic clearance of bacteremia, which would tend to perpetuate bacteremia and increase the opportunity to cause metastatic infection at susceptible sites such as the ascitic collection.

The infrequency of primary peritonitis in forms of ascites other than that due to liver disease emphasizes the importance of intrahepatic shunting in the pathogenesis of this disease. The hepatic reticuloendothelial system is known to be a major site for removal of bacteria from blood, and animal studies have suggested that destruction of blood-borne bacteria by the reticuloendothelial system is impaired in experimental cirrhosis and in alcoholic liver disease. The decrease in phagocytic activity seen in alcoholic cirrhosis is proportional to the severity of the liver disease.

Enteric bacteria may also gain access to the peritoneal cavity by directly traversing the intact intestinal wall. In an animal model, Escherichia coli passes from the bowel into the peritoneal cavity after the introduction of hypertonic solutions into the peritoneum. 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.

In prepubertal girls, the pathogenesis of primary peritonitis is likely related to an ascending infection of genital origin, as suggested by the simultaneous presence of pneumococci in vaginal secretions and peritoneal fluid. Alkaline vaginal secretions that occur in this age group may be less inhibitory to bacterial growth than the acidic secretions of postpubertal females.
TransFallopian spread is also suggested by the development of primary peritonitis in women with intrauterine devices. The route of spread in women with gonococcal or chlamydial perihepatitis (Fitz-Hugh–Curtis syndrome) is presumably via the fallopian tubes and paracolic gutters to the subphrenic space, but it may also be hematogenous.

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 be disseminated hematogenously from remote foci of tuberculosis, most commonly in the lung. Tuberculous peritonitis may become clinically evident after the initial focus has completely healed.

Microbiology. Several decades ago, the organisms reported to cause primary peritonitis in children were Streptococcus pneumoniae and group A streptococci. More recently, the number of nephrotic children with streptococcal peritonitis has declined, and the relative frequency of peritonitis due to gram-negative enteric bacilli and staphylococci has increased. In cirrhotic patients, microorganisms of enteric origin account for ~70% of the pathogens.

E. coli is the most frequently recovered pathogen, followed by Klebsiella pneumoniae, S. pneumoniae, and other streptococcal species, including enterococci. Staphylococcus aureus is an unusual cause of primary peritonitis, accounting for only 2%–4% of cases in most series, but has been noted especially in patients with erosion of an umbilical hernia. Anaerobes and microaerophilic organisms are infrequently reported [4]. Possible explanations include the intrinsic bacteriostatic activity of ascites against Bacteroides species, the relatively high pO2 of ascitic fluid, and the lack of optimal anaerobic bacteriologic techniques used to study patients in the past. The presence of anaerobes correlates strongly with polymicrobial infection. Occasionally, primary peritonitis may also be caused by Neisseria gonorrhoeae, Chlamydia trachomatis, Mycobacterium tuberculosis, or Coccidioides immitis.

Patients who have positive cultures of ascitic fluid with few leukocytes and no clinical signs of peritonitis are considered to have bacterascites. This may represent early colonisation before a host response. Mortality among patients with a low leukocyte response is the same as among those with a greater response. Conversely, several series have identified cases of primary peritonitis with negative ascitic fluid cultures, termed culture-negative neutrocytic ascites [5]. Blood cultures are positive for one-third of these patients. The frequency of negative results of ascitic fluid cultures may be decreased by inoculating blood culture bottles with ascitic fluid at the bedside.

Clinical presentation and evaluation. In children, primary peritonitis is an acute febrile illness often confused with acute appendicitis. Fever, abdominal pain, nausea, vomiting, and diarrhea usually occur, with diffuse abdominal tenderness, rebound tenderness, and hypovolemic or absent bowel sounds. In cirrhotic patients with primary peritonitis, the clinical manifestations may be atypical. Onset may be insidious, with no findings of peritoneal irritation. Fever (temperature of >100°F) is the most common presenting sign, occurring in 50%–80% of cases and even in the absence of abdominal signs or symptoms. Primary peritonitis should always be considered in the differential diagnosis of decompensation of previously stable chronic liver disease, especially hepatic encephalopathy.

Primary tuberculous peritonitis usually is gradual in onset, causing fever, weight loss, malaise, night sweats, and abdominal distension. The abdomen may not be rigid and is often characterized as being “doughy” on palpation. The findings at surgery 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 variable clinical manifestations.

Although the diagnosis of primary peritonitis can be established with certainty only after thorough laparotomy to exclude a primary intraabdominal site of infection, it can usually be surmised from examination of the peritoneal fluid. Fluid obtained at paracentesis should be analyzed for cell count, differential count, and protein concentration, and a gram stain and culture should be performed. Specimens for culture should be sent in an airless, capped syringe or injected directly into aerobic and anaerobic broth culture media; volumes of ≥10 mL will increase the yield of cultures [6].

A gram stain of the sediment is diagnostic when positive but is more commonly negative. Bacteremia occurs in up to 75% of patients with primary peritonitis due to aerobic bacteria, but it is rare in those with peritonitis due to anaerobes. Usually the same organisms isolated from the peritoneal fluid are recovered from the blood.

The ascitic fluid protein concentration may be low in primary peritonitis (<3.5 g/L) because of hypoalbuminemia and dilution of ascitic fluid with transudate from the portal system. The leukocyte count in peritoneal fluid usually is >300/mm3 (>1,000/mm3 in 85%), with granulocytes predominating in >80% of cases. However, the total leukocyte count of some patients with ascites uncomplicated by infection may be similarly elevated. Indeed, an increase in ascitic leukocyte counts has been noted during diuresis in patients with chronic liver disease.

Other parameters of ascitic fluid that may help in diagnosing primary bacterial peritonitis are pH and lactate concentration [7]. An ascitic fluid pH of <7.35 and a lactate concentration of >25 mg/dL are more specific but less sensitive than a leukocyte count of >500/mm3 for diagnostic purposes; using all three parameters together increases the diagnostic accuracy.

In patients with negative ascitic fluid cultures, endoscopic or laparoscopic peritoneal examination and biopsy may be necessary. Peritonitis secondary to other intraabdominal causes should be excluded, and specimens appropriate for fungal and mycobacteriologic cultures should be obtained. In children, if gram-negative organisms, a mixed flora, or no organisms are obtained from peritoneal fluid, full exploratory laparotomy is
generally indicated to rule out possible intraabdominal sources of continuing peritoneal contamination. However, in end-stage cirrhotic patients, exploratory laparotomy may be life-threatening, and the likelihood of finding a primary intraabdominal focus may be small.

Surgery for these patients can be deferred while the response to antimicrobial therapy is awaited. Patients with primary peritonitis usually respond within 48 hours to appropriate antimicrobial therapy. The observation of an exponential rate of decline in the number of ascitic fluid leukocytes after initiation of antimicrobial therapy for primary peritonitis has been found to help differentiate primary from secondary bacterial peritonitis [8].

In patients with a subacute or chronic course of primary peritonitis, other pathogens must be considered, including \textit{M. tuberculosis} or \textit{C. immitis}. The diagnosis of tuberculous peritonitis can usually be made at operation or laparoscopy and confirmed by the histologic characteristics of the peritoneal biopsy specimen and bacteriologic examination of the peritoneal biopsy specimen and fluid. The diagnosis of \textit{C. immitis} peritonitis can be made with a wet mount of ascitic fluid, by finding the organism in culture, or on histologic examination.

**Management and prevention.** 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. Some of the third-generation cephalosporin antibiotics have been demonstrated to be as efficacious as the combination of ampicillin plus an aminoglycoside in primary bacterial peritonitis. They also eliminate the risk of nephrotoxicity, which is sufficiently frequent in this group of patients to warrant avoidance of aminoglycosides if an equally effective alternative antimicrobial regimen can be used.

Other antimicrobial agents such as the broad-spectrum penicillins (e.g., mezlocillin, ticarcillin, and piperacillin), carbapenems (e.g., imipenem), and \(\beta\)-lactam antibiotic/\(\beta\)-lactamase-inhibitor combinations (e.g., ticarcillin-clavulanate and ampicillin-sulbactam) are potential alternatives. If peritonitis develops during hospitalization, the therapeutic regimen, such as administration of an aminoglycoside antibiotic and an antipseudomonal penicillin or cephalosporin in combination, should also be active against \textit{Pseudomonas aeruginosa}.

For those situations in which the gram stain is suggestive of a \textit{Bacteroides} species or polymicrobial peritonitis is evident, antimicrobials with activity against the \textit{Bacteroides fragilis} group and other anaerobic organisms should be added (e.g., metronidazole, clindamycin). The antimicrobial regimen can be modified once the results of the culture and susceptibility tests are available.

In those cases where 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 leukocyte count, should occur after 24–48 hours of antimicrobial therapy if the diagnosis is correct; failure to respond should prompt an examination for additional pathological conditions. Antimicrobial therapy is usually continued for 10–14 days if improvement is noted, but short-course therapy for 5 days has been shown to be as efficacious as the longer course in some patients. Administration of intraperitoneal antimicrobials is not necessary.

Treatment of primary peritonitis is successful in more than one-half of cirrhotic patients, but because of the underlying liver condition, the overall mortality has been reported as high as 95% in some series. Those patients with the poorest prognosis were found to have renal insufficiency, hypothermia, hyperbilirubinemia, and hypoaalbuminemia [9].

Treatment of peritonitis caused by gram-positive organisms, as well as of early infections, has been more frequently successful than treatment of gram-negative or late infections. In neoplastic patients with gram-positive infections or in patients who do not have a preterminal underlying illness, the survival rate is >90%.

Given the common occurrence and high mortality of primary peritonitis in the setting of cirrhosis with ascites, prevention is a desirable strategy. This is particularly true for patients who are awaiting liver transplantation. Selective decontamination of the gut with oral norfloxacin (400 mg daily) has been shown to reduce the incidence of spontaneous bacterial peritonitis. Norfloxacin has the disadvantage of selecting for gram-positive organisms, including \textit{S. aureus}, and quinolone-resistant gram-negative organisms. More recently, trimethoprim-sulfamethoxazole (double-strength, given once daily for 5 days each week) has been shown to reduce the incidence of peritonitis and be well tolerated [10]. A survival-rate advantage has not been demonstrated for any of these preventive regimens.

**Secondary and Tertiary Peritonitis**

**Pathogenesis.** Secondary intraabdominal infection usually is due to spillage of gastrointestinal or genitourinary microorganisms into the peritoneal space as a result of loss of integrity of the mucosal barrier. Examples include appendicitis, diverticulitis, cholecystitis, penetrating wound of the bowel, and perforation of a gastric or duodenal ulcer. Secondary infection is relatively common, taking the form of either generalized peritonitis or localized abscesses. Abscesses may be restricted to the immediate peritoneal space around a diseased intraabdominal organ, such as pericholecystic, periappendiceal, or peridiverticular abscesses, or to certain peritoneal recesses, such as interloop, subdiaphragmatic, subhepatic, lesser sac, or pelvic abscesses.

Peritoneal signs suggestive of appendicitis in immunocompromised patients, e.g., patients with AIDS, organ transplant recipients, and those receiving chemotherapy or corticosteroids for neoplasms (especially myelosuppressive drugs), may be due to typhlitis, an inflammation of the cecum [11]. Cecal ulceration in these patients may progress to perforation and secondary peritonitis with colonic flora. Perforation complicating penetrat-
ing cytomegalovirus enterocolitis has been described as a common cause of acute abdomen in patients with AIDS [12].

Tertiary peritonitis has been conceived as a later stage in the disease, when clinical peritonitis and systemic signs of sepsis (e.g., fever, tachycardia, tachypnea, hypotension, elevated cardiac index, low systemic vascular resistance, leukopenia or leukocytosis, and multiorgan failure) persist after treatment for secondary peritonitis and either no organisms or low-virulence pathogens, such as enterococci and fungi, are isolated from the peritoneal exudate. These organisms may gain access to the peritoneal cavity by contamination during operative interventions, by selection from the initial polymicrobial peritoneal inoculum by antibiotic therapy, or by translocation of bowel flora. Translocation may be promoted by intestinal ischemia, endotoxemia, malnutrition, or proliferation of resistant bowel flora by antibiotic pressure.

The cytokine response in peritonitis has been the subject of a recent excellent review [13]. Undoubtedly, many of the systemic as well as abdominal manifestations of peritonitis are mediated by cytokines, such as TNF, IL-1, IL-6, IFN-γ, and others. Cytokines appear in the systemic circulation of patients with peritonitis and to a much greater extent in the peritoneal exudate [14]. These cytokines are produced by macrophages and other host cells in response to bacteria or bacterial products, such as endotoxin [15], or by tissues traumatized during the operative procedure [16]. Another potential source is direct translocation of cytokines through the intestinal barrier.

Cytokine responses have been studied in the peritoneal exudate in experimental animal models of peritonitis [17–20], in patients with spontaneous bacterial peritonitis [21, 22], in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) [23–25], and in patients with severe secondary bacterial peritonitis who were undergoing planned relaparotomy [14]. Antibodies to TNF have been found to fail to protect against death [26] and failed to reduce serum levels of IL-1 and IL-6 in an experimental model of peritonitis [17, 20, 27]. In contrast, antibodies to endotoxin were found to prevent death in this model, as well as to reduce bacterial numbers in the peritoneal exudate [28]. Antibodies to IFN-γ also afforded a protective effect both in this model of experimental peritonitis and following intravenous injection of endotoxin [29].

Microbiology. With gastrointestinal perforation as the precipitating event, the number and types of microorganisms isolated from the peritoneal cavity depend on the level of the perforation. The stomach in the fasting state contains a sparse microflora of a few relatively more acid-resistant species, e.g., lactobacilli or Candida species. Similarly, the duodenum and proximal small bowel contain a sparse microflora in the fasting state, whereas the colon contains a high microbial density, i.e., about $10^{12}/g$, of which >99.9% are obligate anaerobes, mainly of the B. fragilis group.

E. coli, the predominant colonic facultative anaerobe, is found at counts of $10^{8–9}/g$, while enterococci are less numerous at counts of $10^{5–6}/g$. The characteristic microflora, however, can undergo alteration as a result of the primary disease process or previous antimicrobial therapy. For example, diseases of the stomach that result in obstruction, the loss of gastric acidity (e.g., bleeding, gastric ulcer, or carcinoma), or use of acid-reducing drugs may cause gastric colonization with oral anaerobes, such as non-fragilis Bacteroides and Fusobacterium species and other oropharyngeal organisms, e.g., viridans streptococci, microaerophilic streptococci, Candida species, and lactobacilli.

Gas trectic perforation is associated with either sterile chemical peritonitis or peritonitis due to the above-mentioned pathogens, depending on the underlying gastric condition. Similarly, the normal sparse flora of the small bowel may be altered by gastric disease or small-bowel ileus.

With perforation of the colon, initially enormous numbers (a total of ~$10^{12}/mL$) of the hundreds of different species that constitute the normal colonic microflora spill into the peritoneal cavity. A simplification of the numerous species then occurs, so that once peritoneal infection is established, only about five pathogens on average remain, usually three anaerobic and two aerobic species. In patients with gangrenous or perforated appendicitis, the average number of organisms recovered from clinical specimens has been reported to be as high as 9.8 and 12.7, respectively, with 75% of the flora consisting of anaerobes [30].

The obligate anaerobes isolated have been found to be more oxygen-tolerant and have identifiable virulence factors, as compared with the rest of the obligate anaerobic microflora. B. fragilis is the most frequently isolated anaerobe following colonic perforation, and E. coli is the most frequently isolated facultative anaerobe.

In a now-classic series of experiments in rodents, Weinstein and co-workers clarified the sequence of events that occurs following contamination of the peritoneum with fecal flora [31]. In this model, E. coli is responsible for sepsis and mortality with early peritonitis, and B. fragilis, in concert with E. coli and possibly other microorganisms such as enterococci, is responsible for late peritoneal abscess formation. Such synergy between anaerobes and facultative microorganisms has long been recognized in mixed infections [32].

Some of the microorganisms isolated apparently owe their survival largely to the presence of other bacteria in the polymicrobial infection, such as B. fragilis and E. coli, which if eliminated by specific antimicrobial therapy will result in coincident disappearance of these other microorganisms. The lower intestinal flora can be altered in the severely ill, hospitalized patient under the pressure of antibiotic usage that allows proliferation of multiple-drug-resistant microorganisms, such as P. aeruginosa, Enterobacter species, multiple-drug-resistant enterococci, and Candida species. These microorganisms can then contribute to peritoneal infection that may follow colonic perforation.

The same microorganisms may also be isolated from patients with so-called tertiary peritonitis, i.e., persistent peritonitis in patients with impaired host defenses and multiple organ dys-
function who are unresponsive to initial management [33]. However, monomicrobial infection with microorganisms that have low pathogenicity, such as Candida species, enterococci, and coagulase-negative staphylococci, has been noted even in acute peritonitis in patients with severely impaired defenses [34]. P. aeruginosa usually is thought of as a nosocomial pathogen that emerges under the selective pressure of broad-spectrum antimicrobial agents. In several studies, however, this organism has been isolated in up to 24% of patients with acute community-acquired perforating appendicitis [35, 36].

Although enterococci are found in 20% of intraabdominal infections, their exact role in polymicrobial infection and the need for specific antimicrobial therapy remain controversial. Selective therapy against E. coli and B. fragilis, which has minimal in vitro activity against enterococci, has been found to be sufficient to reduce enterococcal counts [37]. Nevertheless, in animal models of experimental polymicrobial intraabdominal infection, enterococci have been found to be a significant component of the inoculum, which enhances abscess formation, weight loss, bacteremia with B. fragilis and E. coli, and mortality [37, 38].

Similarly, clinical reports have indicated the emergence of enterococcal abscesses and bacteremia after treatment of intraabdominal sepsis with antimicrobial agents that lack significant in vitro enterococcal activity [39–41]. In addition, a recent multicenter study of intraabdominal infection has found that the presence of enterococci in the initial culture, in addition to APACHE II score, independently predicted treatment failure with broad-spectrum antimicrobial regimens that lacked specific enterococcal activity [42]. APACHE II score, age, length of preinfection hospital stay, and postoperative infections predicted the presence of enterococci. It is unknown if initial inclusion of antienterococcal therapy will improve outcome for these high-risk patients.

**Clinical presentation and evaluation.** CT has become invaluable in evaluating patients suspected of having an intraabdominal infection. CT- or ultrasonography-guided aspiration of suspected intraabdominal abscesses has also become standard in evaluating and managing selected patients. Intraabdominal infection encompasses many different pathological and clinical entities that are associated with widely varying mortality rates that range from zero to 60%.

The ability to predict outcome and stratify severity of disease is important for clinical decision-making as well as ensuring comparability in trials that evaluate different management strategies with surgical protocols or antimicrobial agents [43]. Outcome has been found to be related mainly to host factors (e.g., preoperative nutritional status, organ impairment, the severity of the patient’s systemic response, and the premorbid physiological reserves, as predicted by the APACHE II scoring system) rather than to type and source of the infection [44, 45].

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 [46]. This has led to investigation of endotoxin and cytokine levels in circulation to predict outcome. However, the magnitude of levels of endotoxin, TNF, and IL-6, in circulation in patients with peritonitis, has not been invariably related to prognosis [14, 47–51]. It has been suggested that cytokine levels in the peritoneal exudate, rather than the blood, better reflect the severity of the compartmentalized peritoneal infection and predict outcome [14].

**Management and prevention.** A skeptical attitude is necessary when reviewing reports on clinical trials of antimicrobial therapy for intraabdominal sepsis. Surgical therapy alone may be sufficient to cure many otherwise healthy, young patients with intraabdominal infection who have no signs of severe sepsis; even antimicrobial agents to which the pathogens are resistant may be associated with a good outcome for these patients.

To establish a specific role for antimicrobial regimens requires clinical trials with sufficient numbers of high-risk patients whose severity of illness has been stratified by APACHE II scoring. Clinical trials are frequently diluted by low-risk patients, since the sickest patients who would test the efficacy of the antimicrobial agent are often excluded by strict enrollment requirements.

Medical management of secondary peritonitis includes use of antimicrobial therapy and supportive measures to maintain vital functions, e.g., to improve or maintain circulation, nutrition, and oxygenation to vital organs. Antimicrobial agents must penetrate to the site of infection in concentrations that are sufficient to overcome the effects of high bacterial density, metabolic inactivity and slow growth rate of the bacterial inoculum, low pH, low redox potential, necrotic tissue, and bacterial products that may lower the drugs’ activity. For example, aminoglycosides and clindamycin are less active at acidic pH values, aminoglycosides are less active at low redox potentials, and β-lactam drugs are less active against high bacterial densities.

The animal model of intraabdominal sepsis demonstrated the necessity of treating both the facultative enteric gram-negative bacilli, namely E. coli, and the anaerobic gram-negative bacilli, namely B. fragilis. Empirical use of an antimicrobial regimen active against these organisms has been well established. Indeed, the need for intraoperative cultures to document etiological microbes and their antimicrobial susceptibilities has been questioned, because the results are rarely available to influence clinical decisions [52].

Early clinical trials have established the therapeutic regimen of clindamycin plus aminoglycoside as the “gold standard” [53, 54]. Aminoglycosides are frequently underdosed because of fear of nephrotoxicity or because of underestimation of the expanded volume of distribution in critically ill patients with intraabdominal sepsis. Once-daily aminoglycoside therapy—in which the total daily dose is given to patients with normal renal function as a single dose every 24 hours rather than as multiple smaller, divided doses—obeviates these dosing prob-
lems, because both the bactericidal activity and postantibiotic effect of aminoglycosides are concentration-dependent, while their nephrotoxicity is time-dependent. However, too few severely ill patients with intraabdominal sepsis have been studied to allow recommendation of the general use of single daily doses of these drugs.

Regimens in which a third-generation cephalosporin is substituted for the aminoglycoside or metronidazole is substituted for clindamycin compare favorably to the “gold standard.” Resistance, however, emerges readily under selective pressure of antimicrobial therapy with third-generation cephalosporins among certain gram-negative bacilli that produce inducible \( \beta \)-lactamases, such as Enterobacter, Serratia, Citrobacter, Morganella, and Acinetobacter species and \( P. \ aeruginosa \). These organisms have a high spontaneous mutation rate for constitutive production of large amounts of these \( \beta \)-lactamases that confer resistance to all \( \beta \)-lactam drugs, except the carbapenem (imipenem and meropenem) and cefepime, and are poorly antagonized by sulbactam, clavulanic acid, and tazobactam.

Patients likely to be infected with these organisms—e.g., those having prolonged hospital stays, prior antibiotic treatment, postoperative peritonitis, or tertiary peritonitis—are best treated with a regimen that includes imipenem, meropenem, cefepime, a fluoroquinolone, or an aminoglycoside. Resistance among isolates of \( B. \ fragilis \) to metronidazole is rare, while resistance to clindamycin is now unacceptably high in many centers. Furthermore, the relative incidence of \( C. \) difficile—associated diarrhea and colonization was found to be less following use of metronidazole than that following use of clindamycin in a retrospective study [55].

Microaerophilic gram-positive cocci, which are frequent co-pathogens in polymicrobial anaerobic infection, are resistant to metronidazole, unlike clindamycin, so if metronidazole is used it should be combined with an agent active against these pathogens, such as a \( \beta \)-lactam antibiotic other than aztreonam. Aztreonam, fluoroquinolones, and aminoglycosides also lack activity against microaerophilic gram-positive cocci and theoretically may not be optimal agents to combine with metronidazole, although clinical trials of these combinations have been found to be efficacious in intraabdominal infection [56].

Monotherapy with agents that have activity against both aerobes and anaerobes includes the carbapenem imipenem and meropenem and the \( \beta \)-lactam/\( \beta \)-lactamase combinations, such as ampicillin/sulbactam, ticarcillin/clavulanate, and piperacillin/tazobactam. Unacceptably high \( B. \) fragilis resistance to cefoxitin has been found in many centers; cefotetan, another second-generation cephalosporin, is less active than cefoxitin against certain species in the \( B. \) fragilis group.

The duration of antimicrobial therapy after adequate surgery is usually 5–7 days but depends on severity of infection, clinical response, and normalization of the WBC count [53, 57, 58]. Only a short course of antimicrobial therapy (24 hours) is required for sterile peritonitis that occurs in the peritoneal space around an infected but resectable intraabdominal organ, such as the appendix or gallbladder, after resection of the organ. Similarly, contamination of the peritoneum from a defect in the intestinal wall, such as immediately following penetrating abdominal trauma, may also require only operative intervention to remove the diseased organ and a brief course of antimicrobial therapy [53]. Persistent signs of sepsis suggest formation of an intraabdominal abscess that requires drainage, continued contamination of the peritoneum from an inadequately controlled source, superimposed nosocomial infection with a resistant pathogen, or tertiary peritonitis.

Treatment against \( \text{Enterococcus} \) or \( \text{Candida} \) species involved in polymicrobial infections is controversial. Identification of either microorganism in blood cultures, as the sole organism within residual or recurrent intraabdominal infection, or as the predominant pathogen on a gram stain of the appendix or gallbladder is an indication for specific antimicrobial therapy plus adequate surgical debridement. Enterococci have emerged as leading nosocomial pathogens, undoubtedly as a result of their inherent resistance to many commonly used antimicrobial agents and the recent acquisition of resistance to previous standard therapy, i.e., with ampicillin, aminoglycosides, and vancomycin. Only clinically unproven agents to which the strains are susceptible in vitro, such as doxycycline, novobiocin, or quinupristin/dalfopristin, are available as potential therapeutic agents for infection caused by these multiresistant strains of enterococci.

Administration of amphotericin B is standard therapy for invasive candidal infection, although amphotericin lipid complex is an equally efficacious, less nephrotoxic, but more expensive alternative. Azoles such as fluconazole and itraconazole are also less toxic, although no comparative trials for candidal peritonitis have been performed. \( \text{Candida krusei}, \text{Candida tropicalis}, \) and \( \text{Torulopsis glabrata} \) are inherently more resistant to azoles, and resistance to azoles among previously susceptible \( \text{Candida} \) species is increasing.

Although a comprehensive discussion of surgical management of secondary peritonitis is beyond the scope of this review, certain recent trends will be mentioned [59, 60]. Optimal management includes the following: (1) bowel decompression, e.g., by proximal colostomy for perforation, diverticulitis, or colonic carcinoma; (2) closing of traumatic perforations and resection of a diseased, perforated viscus to stop continued peritoneal contamination; and (3) drainage of any purulent collections to reduce the bacterial inoculum and to remove excessive levels of proinflammatory cytokines and other adjuvants, such as fecal matter, food, blood, bile, bullets, or barium.

In the absence of perforation, when the disease process, e.g., acute appendicitis or necrotic bowel, is anticipated to progress, the involved organ is resected. Laparoscopic appendectomy has been recommended for acute appendicitis, with conversion to open appendectomy for perforated appendix or an inflammatory mass, as well as laparoscopic cholecystectomy for acute cholecystitis (with conversion to an open procedure when technical difficulties are encountered).
Abscesses that present as localized peritonitis may be drained percutaneously with the aid of ultrasonography or CT, followed by definitive surgery, if necessary. Percutaneous drainage of a peridiverticular abscess may permit a subsequent one-stage procedure of primary resection and immediate anastomosis.

Peritonitis caused by colonic perforation due to diverticulitis or colon cancer has been treated with one of three procedures, depending on the particular clinical situation: (1) a three-stage procedure, which involves an initial proximal colostomy to decompress the bowel and divert the fecal stream, followed by resection of the diseased bowel, and finally anastomosis to restore bowel continuity several months later; (2) a two-stage procedure, which involves initial resection and temporary proximal colostomy, with either a mucous fistula or a blind pouch (Hartmann’s procedure), followed by anastomosis; or (3) a one-stage procedure of primary resection and immediate anastomosis.

The three-stage procedure has traditionally been reserved for critically ill, high-risk patients; however, the two-stage procedure may be preferred for these patients because it eliminates the source of peritoneal contamination early [61]. The one-stage procedure in the patient with colonic perforation has been questioned because the lumen of the bowel is not cleansed preoperatively and because of the assumed risk of breakdown of the anastomosis in the presence of peritonitis. However, the one-stage primary resection and immediate anastomosis eliminate need for further hospitalization and shorten disability due to a colostomy. Indeed, the one-stage procedure has been shown to be efficacious for the moderate-risk patient with colonic perforation (APACHE II score of ≤15), even in the case of emergency when the bowel has not been cleansed or peritonitis is present [61].

Intraoperative peritoneal lavage with saline, following drainage of purulent peritoneal exudates, fecal matter, food, and other foreign debris, is standard procedure during laparotomy for peritonitis. However, radical peritoneal debridement of all fibrinous deposits on peritoneal surfaces is no longer thought to be effective [62]. Continuous peritoneal lavage for 48–72 hours postoperatively or until the fluid is clear has been studied, but at present the evidence is insufficient to recommend this procedure. Addition of antibiotics or anti-septics to intraperitoneal lavage fluid has also been shown to have no added benefit [53].

Similarly, there has been interest in the role of planned relaparotomies to treat patients with severe peritonitis. Here, the commitment is made at the first operation to perform laparotomies at frequent intervals until the abdomen is macroscopically “clean,” with additional surgical procedures, such as resections, performed as necessary [63]. The abdominal fascia is left open between laparotomies and the defect bridged by saline-soaked gauze or by a temporary abdominal closure device, such as mesh.

These demanding and costly procedures have been complicated by multiple fistulas, wound contamination, incisional her-

nias, and tertiary peritonitis with organisms such as enterococci or Candida species [63–65]. Indeed, repeated entry into the inflamed peritoneum may further escalate the cytokine cascade. A review concluded that in the absence of randomized controlled prospective trials with appropriate stratification of patients by severity of illness, there is insufficient evidence to determine if these procedures improve outcome of severe diffuse peritonitis [66].

**Peritonitis Complicating Peritoneal Dialysis**

*Pathogenesis.* Since its development in the late 1970s, CAPD has provided a safe, cost-effective treatment for end-stage renal disease. Unfortunately, the technique is often abandoned because of its most common complication, peritonitis [67]. The incidence of peritonitis complicating CAPD varies considerably between individual patients and centers. Rates tend to reflect the experience of the center, the specific technology used, and the users’ susceptibility to infection and ability to comply with procedures [68]. Overall, the average incidence of peritonitis is 1.3–1.4 episodes per patient per year [69]. More than half of these episodes are experienced by only 25% of patients.

The two most important routes for development of peritonitis in CAPD patients are (1) transluminal, resulting from a break in sterile technique during dialysate exchange, and (2) contiguous spread, in which microorganisms access the peritoneum along the tract of the dialysis catheter. Less common portals of entry are hematogenous spread from a distant site of infection and direct contamination from the gastrointestinal tract. Diverticular disease of the nonsigmoid colon appears to be a risk factor for acquisition of infection of intestinal origin, presumably through occult microperforations; however, isolation of multiple enteric pathogens from peritoneal fluid, especially anaerobic bacteria, suggests fecal contamination from gross colonic perforations [68].

Microbial factors that may contribute to pathogenesis of peritonitis include ability to grow in dialysis fluids and production of extracellular slime (biofilm). Once organisms gain access to the peritoneal cavity, further growth may depend on their survival in the presence of dialysis fluid. Fresh dialysate solutions are capable of supporting growth of *E. coli* but not that of staphylococci. However, after instillation into the peritoneal cavity, dialysate effluent supports growth of both organisms [69].

Other studies have shown that the growth of *P. aeruginosa* and *E. coli* is enhanced 1,000-fold in dialysis fluids from patients with peritonitis, compared with that in such fluids from uninfected controls [70]. Both staphylococci and *Candida albicans* grow as microcolonies on polymeric surfaces [71]. Surrounding biofilm serves to anchor the organisms and protect them from host defenses and antibiotic activity [72].

The clinical observation that some patients remain free of CAPD-related peritonitis for years suggests that host defense
Clinical presentation and evaluation. Criteria for the diagnosis of CAPD-associated peritonitis are (1) signs and symptoms of peritoneal irritation, (2) cloudy dialysate effluent with a leukocyte count of $>100/\text{mm}^3$, and (3) a positive culture of dialysate fluid. Any two of these criteria may be adequate to establish the diagnosis [82]. Clinical manifestations of peritonitis vary from mild to severe, depending largely on the virulence of the pathogen and the time course of the infection [67]. Generally, turbid dialysate is the first and most common symptom to appear, followed shortly thereafter by abdominal pain and tenderness.

Laboratory evaluation of dialysate effluent is critical to establishing the diagnosis of CAPD-associated peritonitis. A dialysate leukocyte count of $>100/\text{mm}^3$ is the traditional diagnostic value but is not specific. The differential cell count of dialysate may have a better predictive value. In one study, polymorphonuclear leukocytes comprised $>50\%$ of the total cell count (mean, $85\%$) in infected patients, while in uninfected patients the proportion was $<40\%$ (mean, $12\%$) [82]. A preponderance of eosinophils in the fluid is seen in the self-limited condition “eosinophilic peritonitis,” which often follows placement of the Tenckhoff catheter and may represent allergy to the tubing [83, 84].

Peritoneal eosinophilia also occurs with fungal peritonitis or recent intraperitoneal administration of antibiotics. Gram staining of dialysis fluid detects only $20\%$–$30\%$ of peritonitis cases). It warrants special note because of its association with significant morbidity and late complications [75, 76].

Fungi have become an important cause of CAPD-related peritonitis in recent years because of their increasing frequency and problematic management. Although many different fungi have been isolated, including Aspergillus, Mucor, Rhizopus, Alternaria, Fusarium, Penicillium, and Drechslera species, C. albicans accounts for $80\%$–$90\%$ of cases [74, 76]. Risk factors for acquisition of fungal peritonitis are bacterial peritonitis within the preceding month, recent hospitalization, presence of extraperitoneal infection, use of immunosuppressive agents, and concomitant HIV infection, but diabetes mellitus does not pose a special risk [77, 78].

Mycobacteria have been described as pathogens in fewer than $3\%$ of cases of CAPD-related peritonitis, but they may also account for a portion of cases labeled as “culture-negative” [79]. Overall, $86\%$ of mycobacterial isolates reported in the literature have been of group IV (rapid growers), such as M. fortuitum and M. chelonae [80]. One particularly large outbreak involved 17 patients who developed infection with M. chelonae following treatment with contaminated intermittent peritoneal dialysis machines [81]. Other rare causes of peritonitis in patients undergoing CAPD are viruses, algae, and M. tuberculosis.

Factors may also be important in the pathogenesis of this infection [73]. Microbial pathogens that reach the dialyzed peritoneal cavity are removed by three major lines of defense. First, despite the dilution of fibrinogen and coagulation proteins, fibrin trapping and sequestration of microorganisms operate efficiently in the dialyzed peritoneum. Second, removal of the dialysate serves to eliminate or decrease the inoculum of contaminating organisms. Finally, a complex interplay of opsonization, phagocytosis, and intracellular killing by peritoneal macrophages, mesothelial cells, and neutrophils serves to combat bacterial invasion and prevent infection.

Unfortunately, the dialyzed peritoneal cavity is not a supportive milieu for operation of these cellular and immunologic defense mechanisms because of its low pH (5.5–6.0), high osmolality (300–400 mOsmol/kg), and decreased levels of IgG and complement (1% of their normal levels). A correlation between deficiencies in these host defenses and patient risk for peritonitis has not been conclusively identified [73].

Microbiology. In patients undergoing CAPD, peritonitis is usually caused by a single pathogen that originates from the normal flora of the skin or upper respiratory tract. Approximately $60\%$–$70\%$ of cases are caused by gram-positive cocci, $20\%$–$30\%$ by gram-negative bacilli, and the remainder by various other bacteria, fungi, and mycobacteria [74]. Coagulase-negative Staphylococcus is the single most common pathogen, followed by S. aureus and species of Streptococcus. Among the gram-negative organisms, most Enterobacteriaceae species have been associated with CAPD peritonitis, but no single species predominates in all reported series. Although a rare pathogen in other types of peritonitis, P. aeruginosa occurs with relative frequency in CAPD peritonitis ($5\%$–$10\%$ of cases). It warrants special note because of its association with significant morbidity and late complications [75, 76].

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lections are adjusted when the results of cultures and susceptibility tests are known. A single specific agent is adequate treatment in the majority of cases of bacterial peritonitis. P. aeruginosa, however, has been associated with a high therapeutic failure rate and frequent relapses [75, 76]. A synergistic combination of antibiotics, such as an antipseudomonal β-lactam drug plus an aminoglycoside, has been recommended in addition to removal of the dialysis catheter.

Intraperitoneal administration of antibiotics is the preferred method for drug delivery in CAPD-associated peritonitis because it achieves high local concentrations and permits self-treatment by the patient [87–89]. Therapy is usually continued for 10–14 days but may need to be extended with unusually severe or slow-to-resolve infections. Recommendations for specific drug doses and routes of administration are the subject of several reviews [89, 90].

Treatment of fungal peritonitis is controversial because of the lack of controlled studies and the small numbers of cases seen at any single center. Although there are reports of successful treatment with intraperitoneal and/or systemic antifungal agents alone [91, 92], removal of the dialysis catheter is usually prudent to prevent relapse [68, 93]. A short course of systemic amphotericin B (250–500 mg) is often given following catheter removal. Some evidence has suggested that catheter removal alone may be curative in selected patients. Mycobacterial peritonitis also requires removal of the dialysis catheter for cure. Most of these organisms are resistant to conventional antituberculous agents, and susceptibilities vary greatly among the species. Antibiotic selections should be guided by either in vitro susceptibility test results or published recommendations [79–81].

Prevention of peritonitis in patients undergoing CAPD requires intensive education regarding aseptic technique and catheter care. Efforts to reduce the incidence of peritonitis by using oral or intraperitoneal antibiotics have largely been unsuccessful [94–97]. Although a decrease in the number of random positive dialysate cultures has been observed in clinical studies, occurrence of clinical peritonitis was unaffected by prophylactic antibiotics. In addition, topical mupirocin has been used to eliminate nasal colonization with S. aureus but has yet to be shown to significantly impact the incidence of CAPD-related peritonitis [98].

The most significant advances in the prevention of dialysis-related peritonitis involve instrumentation changes, including (1) devices that facilitate connection of tubing, such as titanium adapters; (2) devices that help maintain field sterility during exchanges, such as ultraviolet light systems and in-line filters; and (3) devices that protect intraluminal sterility during exchanges, such as connector systems with disinfectant (Y-connector, O-set). Most such devices have been shown to favorably impact the incidence of peritonitis but add appreciably to the overall cost of CAPD.

References


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