

Pathophysiology, Clinical manifestation and Diagnosis of Peritonitis

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Abstract: Intra-abdominal infection can be caused by various sources. Primary peritonitis or spontaneous bacterial peritonitis (SBP) is an ascetic infection. Peritonitis has been categorized as primary, secondary, tertiary or in patients with continuous dialysis. Frequent symptoms include fever, abdominal pain, nausea, vomiting, and diarrhea, and fever, abdominal pain with altered mental status in patients with cirrhosis. Patients with symptoms of ascites should undergo paracentesis to confirm SBP. Frequently isolated bacterial pathogens include gut flora, coagulase negative staphylococci, and nosocomial multidrug resistant organisms in tertiary peritonitis. Cefotaxime 2 g intravenously every eight hours produce excellent ascetic fluid levels, with supported measures to correct electrolyte imbalance. It is important to diagnose SBP early; delay in diagnosis may result in septic shock. High mortality and decreased survival by approximately 8 percent for each hour of delay in starting antibiotics in patients with septic shock.

Keywords: Primary peritonitis, Pathophysiology, Diagnosis, and Treatment

I. Introduction

Primary peritonitis or spontaneous bacterial peritonitis (SBP) is defined as an ascetic fluid infection without an evident intra-abdominal surgically treatable source [1] Intra-abdominal infections may be caused by a large number of entities, and represent a major cause of morbidity and mortality [2]. 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. Peritonitis complicating dialysis can be considered as an additional category. In the primary variety, the peritoneal infection is not related directly to other intra-abdominal abnormalities. In the secondary variety, an intra-abdominal process, such as a ruptured appendix or a perforated peptic ulcer is evident. 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 secondary peritonitis, and no pathogens or only low grade pathogens (e.g. coagulase negative staphylococci, or nosocomial, frequently multidrug resistant (e.g., enterococci, Candida, Enterobacter spp.) are isolated from the peritoneal exudate [3,4]. Frequent symptoms are fever, abdominal pain, nausea, vomiting and diarrhea [5]. SBP should be suspected in patients with cirrhosis with signs and symptoms such as fever, abdominal pain, altered mental status or hypotension. Patients with ascites should also undergo paracentesis for evidence of SBP [6]. SBP to be differentiated from secondary peritonitis by laparotomy (or laparoscopy) and analysis of ascites fluid [7]. Bacterial pathogens isolated include enteric flora, mainly Escherichia coli [7]. Broad-spectrum therapy is warranted. Cefotaxime 2 g intravenously every eight hours shown to produce excellent ascetic fluid levels, along with supported measures such as vigorous rehydration and correction of electrolyte disturbances [8,9,10]. The paper reviews the pathophysiology, clinical manifestation, diagnosis and treatment of primary or spontaneous peritonitis.

II. Historical cases

Private William Christman, 21 years old died of peritonitis in 1864. Swiss psychiatrist and psychoanalyst Hermann Rorschach, best known for developing a projective test known as Rorschach inkblot test, died of peritonitis in 1882. Henry poet Wadsworth Longfellow also died due to peritonitis in 1882. Famous magician and escape artist Harry Houdini died of peritonitis due to a surprise stomach punch. Man believe that it was a fan who Houdini willingly asked to punch him (as it was indeed part of his act). It, but in reality it was a surprise by a man named Jocelyn Gordon Whitehead. It is possible, however, that punch was only tipping point, and the stomach punches over the years weakened his stomach muscles more and more [11,12].

Actor Rudolph valentine died of peritonitis in 1926 after suffering a ruptured appendix. He also developed pleuritic in his left lung and died several hours after entering a comatose state [13,14] 'Valentino

syndrome' named after him. Rhythm and blues singer Chuck Willis died from peritonitis in 1958 at the peak of his popularity. Beatles Star Ringo (a drummer) contracted peritonitis as a child, falling into coma for three days as a result. Artist George Bellows died of peritonitis in 1925 after failing to tend to a ruptured appendix. Kenneth Pinyan, age 45 died in 2005 in what it became known as the Enumclaw horse sex case. Pinyan had engaged in receptive anal sex with a horse, leading to his death due to acute peritonitis [13,14].

III. Microbial etiology

In cirrhotic patients microorganisms presumably of enteric origin accounts for 69 % of the pathogens [15]. *Escherichia coli* is the most frequently recovered pathogen, followed by *Klebsiella pneumoniae*, *S. pneumoniae*, and other streptococci species, including enterococci [5]. *Staphylococcus 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 [16]. 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* [17].

Three variants of primary or spontaneous peritonitis have been described [18]. One of them, termed monomicrobial non-neutrocytic bacterascites is characterized by ascetic fluid with positive cultures but containing few neutrophils; this condition manifests in patients with clinical findings to peritonitis [19]. It may represent early bacterial colonization before host responses ensue and progresses to spontaneous bacterial peritonitis in 62% to 86 % of cases. The causative bacteria are similar to that seen in classic primary peritonitis, and patients with a low leukocyte responses have been the same mortality rate as patients with greater response [20]. Conversely several series have identified cases of primary peritonitis with negative ascetic fluid cultures, referred to as *culture negative neutrocytic ascites* [21]. Other disorders capable of producing a somewhat similar picture include tuberculous peritonitis, malignancy-related ascites, and 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 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 [21].

Lastly, the third variant of spontaneous bacterial peritonitis, polymicrobial bacterascites [22], 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 ascetic fluid. In this scenario various bacterial forms are seen on the Gram stain or grow on culture of ascetic fluid, which contains less than 250 cells/mm³ [23]. Bacteremia is present in 75% of patients with primary peritonitis caused by aerobic bacteria [15], but is rarely found in patients with peritonitis caused by anaerobes [17]. Usually same organisms isolated from the peritoneal fluid are recovered from the blood [17]. 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 [24].

Secondary peritonitis. Secondary intra-abdominal infection is caused by spillage of gastrointestinal or genitourinary microorganisms into the peritoneal cavity secondary to the loss of integrity of the mucosal barrier. The primary intra-abdominal processes that can give rise to secondary peritonitis are numerous and include diseases or injuries of the gastrointestinal or genitourinary tract, such as perforation of peptic ulcer; traumatic perforation of the uterus, urinary bladder, stomach or large bowel; spontaneous perforation associated with typhoid, tuberculosis, 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 peritoneum disruption of a surgical anastomosis site. Peritonitis is a major hazard of chronic ambulatory peritoneal dialysis (CAPD), used in the management of renal failure [25].

Tertiary peritonitis has been conceptualized as a later stage of in the disease, when clinical peritonitis systemic signs of sepsis 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. In health care-associated intra-abdominal infections, which typically encompass tertiary peritonitis more resistant nosocomial pathogens may also play a major role in the infectious process [26].

IV. Predisposing factors

The common ways peritonitis can occur include: [27].

Primary peritonitis refers to inflammation of the peritoneum from a suspected extra peritoneal source, often via hematogenous spread. Spontaneous peritonitis usually occurs in patients with underlying ascites and is seen most frequently in patients with cirrhosis, nephrotic syndrome, and systemic lupus erythematosus. Peritonitis in

patients with continuous ambulatory peritoneal dialysis (CAPD), and tuberculous peritonitis. **Rupture of viscus** can occur by innumerable means, including a) traumatic injury to the abdomen, including both sharp and blunt trauma. Ulcerated lesions of the colon or upper tract, typhoid fever, necrotizing enterocolitis or perforation of colonic diverticulitis. Ischemia, vascular insufficiency, increased hernias, volvulus, or neoplasia. Ingestion of foreign bodies, toothpicks, bones, pins. **Pelvic inflammatory disease**, including salpingitis and endometritis, can produce localized lower abdominal peritonitis. **Surgical postoperative** leaks and anastomatic breakdowns can occur. Tertiary peritonitis occurs after successful elimination of bacteria by antibiotics. Normally activated host defense systems continue to act through failure of autoregulation, resulting in an auto aggressive devastation of organ system function. The clinical picture mimics occult sepsis. There is no effective therapy [28]. **Rupture from an abscess** can occur, such as of pancreas or rarely a distended gallbladder [28].

V. Pathophysiology

The phrase spontaneous bacterial peritonitis was coined in 1964, the descriptor "spontaneous" was used because the pathogenesis of infection was not apparent [29]. Over the years the void of information has been at least partially filled [30]. One of the early steps in the development of SBP is a disturbance in gut flora with overgrowth and extra intestinal dissemination of a specific organism, most commonly *Escherichia coli* [31,32]. Cirrhosis predisposes to the development of bacterial overgrowth, possibly because of altered small intestinal motility [33], and the presence of hypochlorohydia due to use of proton pump inhibitors [34]. In addition, patients with cirrhosis may have increased intestinal permeability [35]. However, the role of bacterial overgrowth in the pathogenesis of SBP remains unsettled. In one study, small bowel motility and bacterial overgrowth were compared in 20 patients with cirrhosis and history of SBP and 20 patients with cirrhosis without history SBP. The prevalence of bacterial overgrowth was higher in the patients with a history of SBP (70 versus 20 percent); these patients also exhibited more severe small intestinal motility disturbances. In contrast, in another study, the presence of bacterial overgrowth was not associated with development of SBP [34]. 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 liver disease [36].

Enteric bacteria also may gain access to the peritoneal cavity by directly traversing the intact intestinal wall. In an animal model *E. coli* passes from bowel into peritoneal cavity after introduction of hypertonic solutions into the peritoneum [37]. 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 ascetic fluid in most of these patients [17].

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 acidic secretion of postpubertal women. Transfallopian spread also suggested by the development of peritonitis in women with intrauterine devices [38]. 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 sub phrenic space, but it also may be hematogenous. In one man documented with this syndrome *N. gonorrhoeae* was recovered from liver biopsy specimen, and infection presumably spread by means of bacteremia [39].

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 adhesions molecules in the serum and to a much greater extent, in the peritoneal exudate [40]. These cytokines are produced by macrophages and other host cells in response to bacteria or bacterial products, such as toxin. In an experimental model of peritonitis [41], antibodies to endotoxin, but not to TNF- α , were found to prevent death and to 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 [41].

VI. Clinical manifestation

The main manifestations of peritonitis are acute abdominal pain, abdominal tenderness and abdominal guarding which are exacerbated by moving the peritoneum e.g. coughing (forced cough may be used as a test), flexing one's hips, or eliciting the Blumberg sign (a.k.a. rebound tenderness, meaning that pressing a hand on the abdomen elicits less pain than releasing the hand abruptly, which will aggravate the pain, as the peritoneum snaps back into place). The presence of these signs in a patient is sometimes referred to as peritonism [42]. The

localization of these manifestations depends on whether peritonitis is localized (e.g. Appendicitis or diverticulitis before perforation), or generalized to the whole abdomen. In either case, pain typically starts as a generalized abdominal pain (with involvement of poorly localizing intervention of visceral peritoneal layer), and may become localized later (with the involvement of the somatically innervated parietal peritoneal layer). Peritonitis is an example of an acute abdomen [42].

Primary peritonitis is an acute febrile illness often confused with appendicitis in children. Fever abdominal pain nausea and vomiting, and diarrhea usually are 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 typical. The onset may be insidious and findings of peritoneal irritation may be absent in an abdomen distended with ascites. Fever (temperature $>37.0^{\circ}\text{C}$ [$> 100^{\circ}\text{F}$]) is the most common presenting sign, occurring in 50% to 80% of the cases [5,20], and may 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 always should be considered in the differential diagnosis of decompensation of previously stable chronic liver disease [5,20].

It is important to recognize spontaneous bacterial peritonitis early in the course of infection because there is frequently a very short window of opportunity during which to intervene to ensure a good outcome. If the opportunity is missed, shock ensues; followed rapidly multi organ failure [43]. Survival is unlikely in patients who develop shock prior to initiation of empiric antibiotics. One report estimated that survival decreased by approximately 8 percent for each hour of delay in starting antibiotics in patients with septic shock [44].

VII. Diagnosis

Primary peritonitis is diagnosed by ruling out a primary intra-abdominal source of infection. Computed tomography (CT) with oral and intravenous contrast material has greatly enhanced the detection of intra-abdominal sources of peritonitis. Surgery often can be directed towards a potential source of infection identified on the basis of CT findings, rather than by the approach of a full exploratory laparotomy, which was used more commonly in this setting before the availability of CT and was associated with high rates of mortality in certain groups of patients, such as cirrhotic patients. Patients with primary peritonitis usually respond within 48 to 72 hours to appropriate antimicrobial therapy [45]. The observation of an exceptional rate of decline in the ascetic fluid leukocytes after initiation of antimicrobial therapy for primary peritonitis also has been found to help differentiate primary from secondary bacterial peritonitis [46]. 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 [47].

SBP should be suspected in patients with cirrhosis who develop signs or symptoms of fever, abdominal pain, altered mental status, abdominal tenderness, or hypotension. In addition, patients with ascites admitted to the hospital for other reasons should also undergo paracentesis to look for evidence of SBP [6]. The importance of paracentesis was demonstrated in a review of a disease of 17,711 patients with cirrhosis ascites who were admitted to the hospital with primary diagnosis of ascites or encephalopathy [48].

VIII. Treatment, Prognosis and Prevention

Patients with primary of SBP, empiric therapy should be initiated with as soon as possible to maximize the patient's chance of survival [8,9]. However, antibiotics to be given until ascetic fluid has been obtained for culture. Most cases of primary peritonitis are due to gut bacteria such as *Escherichia coli* and *Klebsiella*, though *Streptococcal* and *Staphylococcal* infections can also occur. As a result broad-spectrum therapy is warranted until the results of susceptibility testing is available. Runyon and associates recommend cefotaxime 2 g intravenously every eight hours because it has been shown to produce excellent ascetic fluid levels. In addition to antibiotic therapy, patients with SBP who are taking a nonselective beta blocker should have the medication discontinued, and initiation of supportive measures such as vigorous rehydration and correction of electrolyte disturbances [9, 10].

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% [5]. Subsequent studies however, reported lower mortality rates of 70% and 57%, and 28% and 47%, respectively, died from the primary peritonitis [49,20]. Patients with 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 of less frequency of hepatic encephalopathy. The lowest hospitalization and infection-related mortality rates (37.8% and 2.2%), reported later were attributed to early diagnosis and treatment [44]. However patients suffering severe enough liver disease to develop SBP have poor long-term prognosis; 1- and 2 year mortality rates are 70% and 80% respectively [50].

Prevention. Patients who has survived one episode of primary peritonitis has 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, showed an overall decrease in mortality and a decrease in bacterial infection [51]. One concern with prolonged antibiotic prophylaxis is the potential selection of resistant gut bacterial flora, which can cause spontaneous infection. In randomized trials researches have studied both intermittent and continuous prophylaxis. These include selective decontamination of the bowel with oral norfloxacin (400mg daily), trimethoprim-sulfamethoxazole (double-strength dose given once daily for 5 days each week) and ciprofloxacin (a single weekly dose of 750mg or 500 mg daily) [52]. Most who have had one or more episodes of spontaneous bacterial peritonitis. A similar approach to prevent infection in patients awaiting liver transplantation is often undertaken, although randomized trials supporting this practice are lacking [52]. Guidelines for the use of preoperative antimicrobial prophylaxis recommendations include the use of prophylactic cefazolin in esophageal, gastroduodenal surgery, high risk individuals those with morbid obesity and those undergoing biliary tract surgery and for those individuals older than 70 years of age. Postoperative doses were suggested to be unnecessary [53].

IX. Conclusion

Peritonitis is an inflammation of the peritoneum usually occurs in patients with underlying causes frequently cirrhosis, ascites, nephrotic syndrome, patients on continuous dialysis, rupture of viscus, ulcerated lesions of colon, and pelvic inflammatory disease. Early diagnosis and empiric antibiotic therapy is important. Survival is decreased if delay in starting antibiotics in patients with septic shock.

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