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PRIMARY PERITONITIS

SUMMARY

Due to its relatively low incidence, unspecific etiopathogenesis, often vague simptomatology and complex multidisciplinary treatment primary peritonitis remains a diagnostic and therapeutic challenge for a physician, especially for the general surgeons who most commonly deal with intraabdominal infections that are the result of a hollow viscus perforation (secondary peritonitis). Primary peritonitis as challenging multidisciplinary clinical entity and possible surgical problem is under review in presenting paper. The definition, incidence, pathogenesis, microbiological etiology, clinical presentation, diagnosis, treatment and prevention are analyzed in order to provide with updated information most valuable for adequate management of this serious clinical condition.

Key words: **primary peritonitis, cirrhosis, ascites**

INTRODUCTION

Peritonitis implies an inflammatory response of the abdominal cavity peritoneal layer in terms of an activation of local mediator cascades by different stimuli (1). Viral, bacterial and chemical agents and trauma may be involved in the etiopathogenesis of peritoneal inflammation. In surgical practice, trauma, bacterial and sometimes chemical agents are the most frequent causes of peritonitis (1,2). The terms *intraabdominal infection* and *abdominal sepsis* are often used to describe peritonitis of an infectious etiology. Peritonitis is classified into three specific types, depending on the clinical scenario: *primary, secondary* or *tertiary*, each representing a distinct clinical entity. In most of the different forms of peritonitis there is the main, surgically relevant underlying problem associated with abdominal sepsis. However, peritonitis is inhomogenous in regard to the cause, pathophysiology and severity. Considering that these aspects influence the choice of therapy and prognosis, each individual case of peritonitis needs profound consideration. Due to its relatively low incidence, unspecific etiopathogenesis, often vague simptomatology and complex multidisciplinary treatment, *primary peritonitis* remains a diagnostic and therapeutic challenge for a physician, especially for the general surgeons who most commonly deal with intraabdominal infections that are the result of a hollow viscus perforation (secondary peritonitis). Primary peritonitis as challenging multidisciplinary clinical entity and possible surgical problem is under review in presenting paper.

DEFINITION AND INCIDENCE

Primary peritonitis is an infection of the peritoneal cavity not directly related to other intraabdominal abnormalities. This term describes a peritoneal infection without an evident source. Since the vast majority of cases are due to bacterial

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infection, this condition is also commonly known as *spontaneous bacterial peritonitis*. In primary peritonitis, bacteria invade the peritoneal cavity from a suspected extraperitoneal source via a hematogeneous, lymphogeneous or luminal route.

Although a rare condition, in adults primary peritonitis develops in up to 25% of patients with alcoholic cirrhosis. Also, it has been reported to occur in patients with postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, metastatic malignant (especially liver) disease, systemic lupus erythematosus, lymphedema and rarely in adults with no underlying disease (3). The presence of ascites appears to be a common link among these various conditions (Table 1).

Table 1. Risk factors for ascitic fluid infection

- Severe liver disease (cirrhosis Child-Pugh C)
- Low total protein concentration in ascitic fluid (<1,5gm/dL, especially if <1,0gm/dL)
- Esophageal variceal or gastrointestinal bleeding
- Urinary tract infection
- Intestinal bacterial overgrowth
- Previous spontaneous bacterial peritonitis
- Iatrogenic factors (urinary bladder and intravascular catheters etc.)

Today, spontaneous peritonitis in adults due to liver cirrhosis is considered to be an episode of liver failure indicating the necessity of liver transplantation (4). Primary bacterial peritonitis is also the most common complication in patients with chronic renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD) and is considered to be a distinct entity. Overall, the average incidence of this infection is 1,3-1,4 episodes per CAPD patient per year (5). More than half of these episodes are experienced by only 25% of patients. In children, in the preantibiotic era primary peritonitis accounted for about 10% of all pediatric abdominal emergencies. It now accounts for less than 1-2% (6). 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.

PATHOGENESIS

Although the route of infection in primary peritonitis is usually not apparent, it 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 (Table 2).

Table 2. Pathogenesis of primary peritonitis

Primary peritonitis	Bacterial invasion - Hematogenous - Lymphatic -Intraluminal (transmural)

In cirrhotic patients the hematogenous route is most likely: microorganisms 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 destruction of blood-borne bacteria by the reticuloendothelial system is impaired in animal 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. 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.

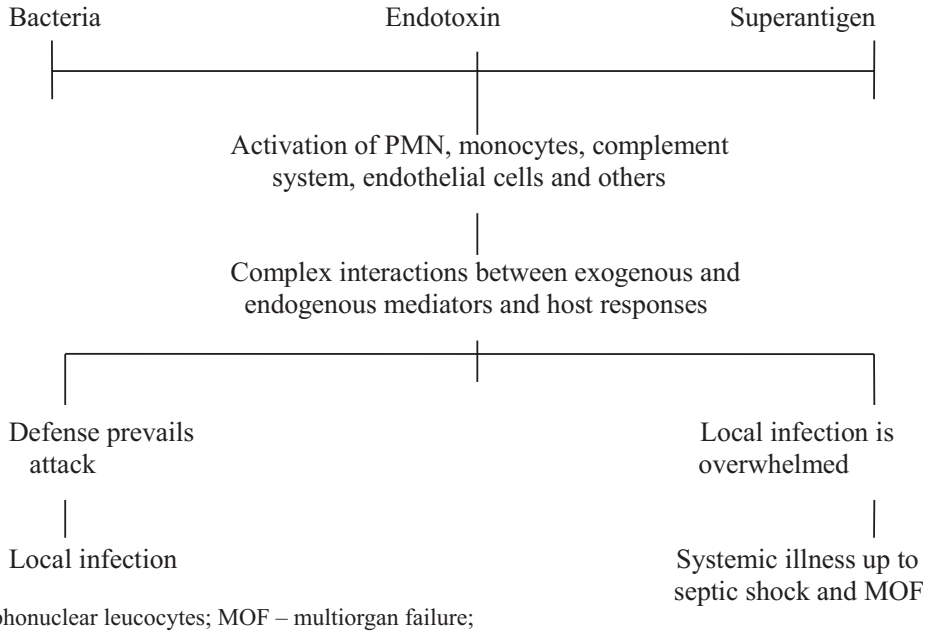
In prepubertal girls, the pathogenesis of primary peritonitis is likely related to an ascending infection of genital origin, as suggested by the simultaneous presence of pneumococci in vaginal secretions and peritoneal fluid. Alkaline vaginal secretions that occur in this age group may be less inhibitory 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.

Tuberculous patients are considered to be a distinct category of patients exposed to the risk of primary peritonitis development. Although tuberculous peritonitis may result from direct entry into the peritoneal cavity of tubercle bacilli (from the lymph nodes, intestine or genital tract in patient 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. Pathophysiology of peritonitis includes complex interactions between various triggers of the mediator cascade, endogenous mediators and host responses *(Figure 1)*.

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 colonization of ascites before a host response. Mortality among patients with a low leukocyte response is the same as among those with a



PMN – polymorphonuclear leucocytes; MOF – multiorgan failure;

Figure 1. Pathophysiology of peritonitis (endotoxin: trigger of the mediator cascade)

MICROBIOLOGY

Primary peritonitis represent an infection that is microbiologically distinct from other peritoneal infections because it is usually monomicrobial. In nephrotic children the most frequent primary peritonitis are due to gram-negative enteric bacilli and staphylococci, while streptococcal peritonitis has declined. In cirrhotic patients, microorganisms of enteric origin account for approximately 70% of the causative pathogens. E.coli is the most frequently discovered 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, but has been noted especially in patients with erosion of an umbilical hernia. Anaerobes and microaerophilic organisms are infrequently reported (7). 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 greater response. Conversely, several series have identified cases of primary peritonitis with negative ascitic fluid cultures, termed *culture-negative neutrocytic ascites* (8). Blood-cultures are positive in 1/3 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 DIAGNOSIS

In children, primary peritonitis is an acute febrile illness often confused with acute appendicitis. Fever, abdominal pain, nausea, vomiting and diarrhea usually occur, with palpatory diffuse abdominal tenderness, rebound tenderness and hypoactive or absent bowel sounds. In cirrhotic patients the clinical manifestation of primary peritonitis may be atypical. Onset may be insidious, without findings of peritoneal irritation. Fever (>38,5º) is the most common presenting sign, occuring 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 is usually gradual in onset, with 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 diagnostic surgery or laparoscopy consist of multiple nodules scattered over the peritoneal surface and omentum. Adhesiones and a variable amount of peritoneal fluid are usually present. Similarly, Coccidioides 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 (Table 3).

Table 3. Indications for diagnostic paracenthesis

- New onset of ascites
- Hospital admission in a patient with known ascites
- Clinical deterioration (onset of abdominal symptoms) in a patient with cirrhosis and ascites
- Azotemia
- Hepatic encephalopathy
- Gastrointestinal bleeding
- Deterioration in laboratory test values (leucocytosis etc.)

Fluid obtained at paracentesis should be analyzed for cell count, differential count and protein concentration and a gram-staining and culture should be performed (Table 4). Specimens for culture should be sent in an airless, capped syringe or injected directly into aerobic and anaerobic broth culture media. Volumes of >10ml 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 discovered in the blood. The ascitic fluid protein concentration may be low (<3,5g/L) because of hypoalbuminemia and dilution with transudate from the portal system. The leukocyte count in peritoneal fluid usually is >300/mm³ (>1000/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. An ascitic fluid pH of <7.35 and a lactate concentration of >25mg/dL are more specific but less sensitive than a leukocyte count of >500/mm³ for diagnostic purposes. Still, using all three parameters together increases the diagnostic accuracy.

Table 4. Analysis of ascitic fluid

Routine	Optional	Unusual
-Total protein	- Gram stain	- Cytology
-Albumin	- Amylase	- Acid-fast bacillus smear and culture
-Cell count with WBC differential	- LDH	- Triglycerides
-Culture in bllood culture bottles	- Glucose	

In patients with negative ascitic fluid cultures, laparoscopic peritoneal examination and biopsy may be necessary. Peritonitis secondary to other intraabdominal causes should be excluded and specimens 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 rapid decrease of the number of ascitic fluid leukocytes that can be observed after initiation of antimicrobial therapy for primary peritonitis has been found to help differentiate primary from secondary bacterial peritonitis (9).

In patients with a subacute or chronic course of primary peritonitis, other pathogens must be considered, including M.tuberculosis or C.immitis. The diagnosis of tuberculous peritonitis can usually be made at operation or laparoscopy and confirmed by the histologic characteristics and bacteriologic examination of the peritoneal biopsy specimen and fluid. The diagnosis of 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

Traditional therapy for peritonitis is presented in Table 5. 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 β-lactam antibiotic/β-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 Pseudomonas aeruginosa. For those situations in which the gram stain is suggestive of a Bacteroides species or polymicrobial peritonitis is evident, antimicrobials with activity against the 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 (Table 6).

In 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.

Table 5. Traditional therapy for peritonitis

- Alimentary decompression
- Fluid resuscitation
- Systemic antibiotics
- Contamination source control

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 hypoalbuminemia (10). 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 nephrotic patients with gram-positive infections or in patients who do not have a preterminal underlying illness, the survival rate is >90%.

Table 6. Surgical Infection Society guidelines for antibiotic treatment of established peritonitis

Single agents:
- ampicillin-sulbactam
- cephalosporins (according to antibiogram)
- imipenem-cilastatin
- meropenem
- piperacillin-tazobactam
- ticarcillin-clavulanic acid

Combination regimens:
- aminoglycoside plus antianaerobe
- aztreonam plus clindamycin
- cefuroxime plus metronidazole
- ciprofloxacin plus metronidazole
- III and IV generation cephalosporins plus antianaerobe

Considering 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 (400mg daily) has been shown to reduce the incidence of spontaneous bacterial peritonitis. Norfloxacin has the disadvantage of selecting for gram-positive organisms, including S.aureus and quinolone-resistant gram-negative organisms. More recently, trimethoprim-sulfamethoxazole (double-strenght, given once daily for 5 days each week) has been shown to be well-tolerated and reduce the incidence of peritonitis (11). A survival-rate advantage has not been demonstrated for any of these preventive regimens.

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PRIMARNI PERITONITIS

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SAŽETAK

Zahvaljujući relativno niskoj incidenci, nespecifičnoj etiopatogenezi, često neodređenoj simptomatologiji i kompleksnom multidisciplinarnom lečenju, primarni peritonitis i dalje predstavlja dijagnostički i terapijski izazov za kliničara, a posebno za opšte hirurge koji najčešće leče intraabdominalne infekcije, koje nastaju kao rezultat perforacije šupljih trbušnih organa (sekundarni peritonitis). Prezentovani rad predstavlja pregled literaturnih podataka o primarnom peritonitisu kao izazovnom multidisciplinarnom kliničkom entitetu i mogućem hirurškom problemu. Data je definicija i analizirani su podaci i dileme o incidenci, patogenezi, mikrobiološkim uzročnicima, kliničkoj prezentaciji, dijagnozi, lečenju i prevenciji primarnog peritonitisa u cilju pružanja savremenih informacija i stavova najznačajnijih za adekvatan tretman ovog ozbiljnog kliničkog stanja.

Ključne reči: **primarni peritonitis, ciroza, ascites**