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Invited critical review

Laboratory diagnostics of spontaneous bacterial peritonitis

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ABSTRACT

The term peritonitis indicates an inflammatory process involving the peritoneum that is most frequently infectious in nature. Primary or spontaneous bacterial peritonitis (SBP) typically occurs when a bacterial infection spreads to the peritoneum across the gut wall or mesenteric lymphatics or, less frequently, from hematogenous transmission in combination with impaired immune system and in absence of an identified intra-abdominal source of infection or malignancy. The clinical presentation of SBP is variable. The condition may manifest as a relatively insidious colonization, without signs and symptoms, or may suddenly occur as a septic syndrome. Laboratory diagnostics play a pivotal role for timely and appropriate management of patients with bacterial peritonitis. It is now clearly established that polymorphonuclear leukocyte (PMN) in peritoneal fluid is the mainstay for the diagnosis, whereas the role of additional biochemical tests is rather controversial. Recent evidence also suggests that automatic cell counting in peritoneal fluid may be a reliable approach for early screening of patients. According to available clinical and laboratory data, we have developed a tentative algorithm for efficient diagnosis of SBP, which is based on a reasonable integration between optimization of human/economical resources and gradually increasing use of invasive and expensive testing. The proposed strategy entails, in sequential steps, serum procalcitonin testing, automated cell count in peritoneal fluid, manual cell count in peritoneal fluid, peritoneal fluid culture and bacterial DNA testing in peritoneal fluid.

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1. Introduction

The peritoneum is the serous membrane that forms the lining of abdominal cavity, covers and supports most of intra-abdominal organs, and also serves as a conduit for their blood and lymph vessels and nerves. From a biological perspective, the peritoneal membrane is a sterile, semi-permeable membrane with multiple pores, which allows a flux of solutes and water from the vascular system to the peritoneal cavity and vice versa, mainly through a diffusion mechanism [1].

The term peritonitis designates an inflammatory process involving the peritoneum. Although peritonitis may be occasionally sterile (e.g., due to chloridric acid or to bile salts), the most frequent cause is represented by infections. Bacterial peritonitis (BP) is hence

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defined as an inflammation of the serous membrane that covers the viscera and the peritoneal cavity due to bacterial contamination. It is conventionally classified as (i) primary, or spontaneous BP (SBP), when a bacterial infection spreads to the peritoneum across the gut wall or mesenteric lymphatics or – less frequently – from hematogenous transmission in combination with an impaired immune system and in absence of an identified intra-abdominal source of infection or malignancy; (ii) secondary BP, when the infection is a consequence of a gastro-intestinal perforation; and (iii) tertiary or recurrent BP, defined as persistence or recurrence of intraabdominal infection in the presence of apparently appropriate therapy [1,2]. The most important infective agents involved in different types of peritonitis are reported in Table 1. Due to the remarkable differences existing in clinical significance and management of the aforementioned forms of BP (i.e., the secondary and tertiary forms of PB are mainly of surgical competence), this article is focused on clinical and laboratory diagnostics of SBP.

1.1. Primary peritonitis or spontaneous bacterial peritonitis

SBP, firstly described in 1971 by Conn and Fessel [3], is the infection of a previously sterile ascitic fluid that frequently represents a complication of liver cirrhosis. It affects about one third of cirrhotic patients [4,5], in absence of visceral perforations or other intra-abdominal infections, as abscess, acute pancreatitis or cholecystitis [6,7]. SBP is characterized by poor outcome and high mortality, ranging from 10 to 50% at the first in-hospital episode [8–10]. Bacterascites, which is instead defined as the presence of a positive culture of ascitic fluid without an increased peritoneal leukocyte count, has a much lower prevalence, ranging from 2 to 3% in outpatients, but reaching 11% in hospitalized patients [5].

Portal hypertension, changes in intestinal flora and impaired immunity, typically involving cirrhotic patients, are the main causes of bacterial overgrowth and translocation from the intestinal lumen to mesenteric lymph nodes or other extraintestinal organs and sites [6,11–13]. Changes in intestinal flora and bacterial overgrowth are represented mainly by the increased growth of Gram-negative aerobic bacilli from Enterobacteriaceae family (such as *Escherichia coli* and *Klebsiella* spp.) [14–16], due to failure of intestinal clearance [17], and in association with impaired small-bowel motility and decreased intraluminal concentration of bile salts [18,19]. Only a limited number of intestinal bacteria can efficiently translocate from the lumen of the gut into mesenteric lymph nodes, and these include *E. coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae [20–22].

Gram-positive bacteria are typically involved in 23–40% of SBP and comprise *Streptococci* and (less often) *Staphylococci*, whereas anaerobic bacteria (e.g., *Bacteroides*, Clostridia, *Lactobacillus*) are more frequently isolated from multiple organisms SBP [23]. *Listeria monocytogenes* has been only occasionally identified in cases of SBP [24,25]. The third factor predisposing to SBP in cirrhotic patients is the impaired immunity, which is characterized by reticuloendothelial system depression, leukocyte dysfunction, and altered ascitic fluid defenses [8,16].

2. Clinical signs and symptoms

Since infections in the peritoneum can be generalized or localized, the signs and symptoms of peritonitis are then highly variable. In a classical secondary peritonitis, these include swelling, bloating and tenderness in the abdomen. The pain may vary from dull aches to severe, localized or diffuse, sharp pain, and is frequently accompanied by fever (many of patients have a temperature that exceeds 38 °C, although patients with severe sepsis may become hypothermic) and chills, loss of appetite, thirst, nausea and vomiting [26–28]. Abdominal pain is more intense with motion or touch and is often lessened when patients take a fetal position [29]. Obstruction to gas or stool, oliguria, low blood pressure and tachycardia may occur in the most severe forms of generalized peritonitis.

The clinical presentation of SBP is highly variable and this condition may manifest as a relatively insidious colonization – without signs and symptoms – or it can rapidly develop as a septic syndrome [6,30]. Since suggestive symptoms and signs are frequently absent in patients with SBP, the available guidelines suggest a diagnostic paracentesis in all ascitic patients admitted to the hospital [5,31–33]. Very rarely, hepatic encephalopathy may be the only manifestation of SBP. Also in tertiary peritonitis the presenting symptoms are nonspecific and insidious in onset (e.g., low-grade fever, anorexia, weight loss) [26].

3. Complications and prognosis

Despite remarkable developments in earlier detection, medical and surgical therapy, the average mortality rate of SBP remains elevated, approaching 30% [34,35], and ranging from <5% in low-risk patients to approximately 90% in those at higher risk. Most information on the predictive factors associated with poor outcome comes from studies carried out in cirrhotic patients with SBP. In this setting well recognized indicators of mortality include advanced age [36], child score >2, the presence of bacteremia [37], lack of infection resolution, modification of antibiotic treatment and culture positivity [9,38], nosocomial origin [39], and the presence of *CARD15/NOD2* (nucleotide-binding oligomerization domain-containing protein 2/caspase recruitment domain-containing protein 15) gene variants [40], along with increased concentrations of

Table 1
The most important infective agents involved in different types of peritonitis.

	Spontaneous bacterial peritonitis	Secondary peritonitis	Tertiary peritonitis
Aerobic	Gram-negative	Gram-negative	Gram-negative
	Escherichia coli	*Escherichia coli*	*Pseudomonas aeruginosa*
	Klebsiella	*Enterobacter*	Enterobacter
		Klebsiella	
		Proteus	
		Fusobacterium sp.	
		Pseudomonas aeruginosa	
		Chlamydia trachomatis	
	Gram-positive	Gram-positive	Gram-positive
	Streptococci	*Streptococci*	*Enterococci*
	Staphylococci	*Enterococci*	*Staphylococcus*
	Listeria monocytogenes	*Staphylococci*	
		Listeria monocytogenes	
Anaerobic	*Bacteroides*	*Bacteroides* (*B. fragilis*)	
	Clostridia	Eubacteria	
	Lactobacilli	Clostridia	
		Peptostreptococci	
		Peptococci	
Fungi			*Candida*