Turk J Med Sci
33 (2003) 131-134

Review

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Peritoneal Defense Mechanisms

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Received: April 30, 2003

Peritonitis can be divided into primary and secondary forms. Primary peritonitis occurs either spontaneously or secondary to infection of an intraperitoneal catheter, i.e. for dialysis. It is usually caused by a single organism. Secondary peritonitis is the sequelae of a perforation of the gastrointestinal tract caused by trauma or disease or secondary to the infection of an intraabdominal organ. For practical purposes secondary peritonitis should be divided into a community acquired, i.e. due to perforated diverticulitis, and nosocomial form, i.e. due to anastomotic dehiscence. Recently, tertiary peritonitis has been described as a separate entity. It is characterized by a prolonged course, opportunistic causative organisms, minimal local reaction, and pronounced systemic inflammatory response syndrome (1). If locally contained, all forms of peritonitis can result in abscess formation (Table 1).

Table 1. Classification of intraabdominal infections.

1. primary peritonitis
   a) spontaneous
   b) catheter associated
2. secondary peritonitis
   a) community acquired
   b) nosocomial
3. tertiary peritonitis
4. intraabdominal abscess

Regardless of the cause, the presence of bacteria in the peritoneal cavity triggers a number of local and systemic responses of the host aimed to fight the invading micro- organisms, but can also lead to deleterious local and systemic sequelae for the host. This short review is concerned with the nature, properties and interaction of the causative bacteria, the local and systemic immune response, the barrier function of the peritoneum, and the role of fibrin in the local host defense. This paper will concentrate on secondary peritonitis.

Bacteriology of intraperitoneal infections

While primary peritonitis is caused by a single organism, the bacteriology of secondary peritonitis is more complex. The causative bacteria originate from the gastrointestinal tract and therefore secondary peritonitis is always a polymicrobial infection. However, after the release of the bacteria into the peritoneal cavity a selection from the over 400 species present in the intestinal flora occurs and only a limited number of bacterial species, usually three to five, are found in microbiological specimens of patients with peritonitis or intraabdominal abscesses. One can distinguish three groups of bacteria: Gram-positive aerobes, Gram-negative aerobes, and anaerobes. The localization and the nature of primary focus of the intraperitoneal infection determines the initial bacteriology. While peritonitis due to perforations of the upper gastrointestinal tract initially shows few, usually Gram-postive aerobe organisms, perforations of the colon result immediately in peritonitis due to a mixed aerobic/anaerobic flora. The nature of the underlying disease also influences the initial bacterial flora of peritonitis. Suppurative inflammations lead to a predominantly aerobic flora, whereas gangrenous inflammations result in a mixed aerobic/anaerobic flora. After some time has elapsed, however, the bacteriology of intraperitoneal infections becomes uniform (Table 2). This is due to the always present ileus and the resulting bacterial overgrowth and the translocation of bacteria from the bowel lumen into the free peritoneal cavity (see below). Different bacterial species act synergistically during peritonitis. That is to say, together they create a disease that cannot be caused by a single organism alone.

Table 2. Bacteriology of peritonitis (n = 385) (7).

Streptococci	108 (28%)	Bacteroides/Prevotella spp.	288 (72%)
Enterococci	66 (17%)	B. fragilis	153 (38%)
Staphylococci	29 (7%)	anaerobic cocci	97 (25%)
E. coli	235 (60%)	Eubacteria	94 (24%)
Enterobacter/Klebsiella spp.	101 (26%)	Clostridia	67 (17%)
Proteus spp.	87 (22%)	Propionobacteria	36 (9%)
Pseutomonas spp.	30 (8%)	Fusobacteria	34 (8%)

To create an intraperitoneal infection that resembles the clinical picture of peritonitis a combination of Gram-negative aerobic and anaerobic bacteria is necessary in animal experiments (2). Bacteria found in secondary peritonitis are facultative, not obligatory pathogens. They contain certain constitutive structural elements called pathogen associated molecular patterns (PAMPs) such as lipopolysaccharide, peptidoglycan, lipoteichoic acid, mannans, bacterial DNA, and double-stranded RNA, which are responsible for the deleterious effects on the host (3).

Innate immunity and inflammation

The PAMPs are recognized by pattern recognition receptors which are present on the surface of many immunologic effector cells for the peritoneal cavity the most important are macrophages. They cause the effector cells to function immediately without prior proliferation, thus allowing a rapid immunologic response. A discussion of the structural and functional properties of the pattern recognition receptors is beyond the scope of this review. For this discussion, however, it is important that they can be functionally divided in secreted, endocytic, and signalling pattern recognition receptors. Secreted receptor molecules function as opsonins binding to the bacterial cell wall and facilitating the destruction of the cell by complement and its phagocytosis by neutrophils and macrophages. Endocytic receptor molecules are present on the surface of phagocytotic cells and mediate phagocytosis and bacterial killing. Signaling receptor molecules induce the expression of various immune-response genes triggering the inflammatory cytokine cascade (3).

These events lead to a local as well as a systemic inflammatory response. The initial step for the local inflammatory response is the migration of neutrophils from the vessel lumen into the peritoneal cavity. This process starts with the marginalization and slowing of the flow velocity of the neutrophils, both of which are mediated by L-selectin binding to certain carbohydrates on the surface of the endothelial cells. While being activated the neutrophils become fixed to the endothelial cell through binding between its integrin and the E-selectin of the endothelial cell. After diapedesis through the vessel wall the phagocyte migrates to the site of infection along a concentration gradient of chemoattractants such as complement and inflammatory cytokines where they phagocytize and kill the bacteria. (4). After the bacterium is completely engulfed by the phagocyte the actual killing of the bacterium is brought about by highly active oxygen compounds released from a vacuole in the phagosome.

During these events many endogenous mediators are activated, some of which have already been mentioned and which are listed in Table 3. These endogenous mediators act on blood vessels leading to vasodilation, vasoconstriction, cellular aggregation, and functional impairment of endothelial cells. In addition, they depress myocardial function and cause myocardial dilatation. It has been thought in the past that the cardiac damage was

Table 3. Endogenous mediators.

Inflammatory cytokines
Platelet activating factor
Endorphins
Nitrous oxide
Arachidonic acid metabolites
Complement
Kinines
Coagulation factors

mediated by a special protein termed myocardial depressant factor. However, it is likely that this protein is identical to the tumor necrosis factor. Finally, the endogenous mediators of sepsis interfere with the function of parenchymateous organs and lead to metabolic derangements (5). This generalized activation of inflammation has been called systemic inflammatory response syndrome (SIRS). If not reversed it will progress to septic shock and/or multiple organ failure (6).

Barrier function of the peritoneum

The peritoneum has a surface area of 1.7 m^2, roughly equivalent to that of the body. Most of the peritoneum behaves as a passive semipermeable membrane allowing a bidirectional flow of water and most solutes. Fluid exchange and solute flow are functionally related to the membrane area, changes in membrane permeability, and local blood flow. The inflammatory process of peritonitis causes a rapid shift from the intravascular space to the interstitial space and in the peritoneal cavity (7). The ileus, which always accompanies peritonitis, causes additional fluid shifts by losses into the bowel lumen and lack of reabsorption of proximal secretions. All these events are potentiated by the generalized damage to the barrier function caused by inflammatory response syndrome.

The loss of fluid into the interstitial space, the peritoneal cavity and the bowel lumen results in hypovolemia and increased intraabdominal pressure. The normal intraperitoneal pressure is under 10 mmHg. An elevation above 10 mmHg is called abdominal compartment syndrome. The relationship between volume and pressure in the peritoneal cavity is not linear, but asmptotic. When a certain critical volume has been reached small additional increases in volume will lead to a disproportionate increase in pressure (Figure). Mildly elevated intraabdominal pressure (10-20 mmHg) results in impaired visceral blood flow and a mechanical embarrassment of pulmonary function. Moderately elevated intraabdominal pressure (20-40 mmHg) leads in addition to a decrease in venous return and thus to impairment of myocardial function and oliguria. Finally, intraabdominal pressure above 40 mmHg will lead to anuria (8).

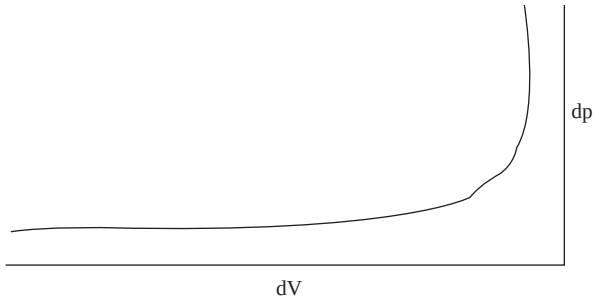

Figure. Relationship between intraperitoneal volume and intraperitoneal pressure.

While the entire peritoneum acts as a semipermeable membrane for fluid and solutes, the passage of particulate matter such as bacteria is restricted to certain areas under normal conditions. Particulate matter can be absorbed through stomata between the mesothelial cells of the diaphragmatic peritoneum directly into specialized lymphatic channels called lacunae which underlie a fenestrated mesothelial basement membrane. These stomata are elastic and allow the passage of particles up to 10 µ in diameter, which include bacteria 0.5-2 µ in diameter. During expiration the stretching of the diaphragm causes a rapid flow into the lacunae, while during expiration the contraction of the diaphragm forces the fluid into the lymphatics. This mechanism affords a rapid initial clearing of bacteria from the peritoneal cavity (7).

A reverse process can be observed during shock and in the presence of severe inflammation of the peritoneum, i.e. abscesses. Under these conditions the normal peritoneum becomes permeable to bacteria, which then translocate from the bowel lumen into the peritoneal cavity or into abscesses (9).

Fibrin and adhesion formation

The normal peritoneum has fibrinolytic activity that decreases after laparotomy and is completely abolished during peritonitis. The loss of fibrinolytic activity is probably due to an upregulation of transforming growth factor beta-1 (TGF-β1), a potent mitogen, chemoattractant, and stimulant of collagen synthesis (10). The lack of fibrinolytic activity results in the persistence of fibrin, which entraps bacteria leading on one hand to the localization of the infection but on the other to the protection of the bacteria from host defenses. The bacteria in a fibrin clot and the numerous surrounding phagocytotic cells release exoenzymes and highly active oxygen compounds, which damage the

tissue. This constitutes the basis for the development of abscesses, the internal milieu of which are characterized by a low pH, a low oxidation/reduction potential, decreased bacterial killing by neutrophils and a high concentration of bacteria and their exoenzymes (11).

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