REVIEW ARTICLE

THE PATHOPHYSIOLOGY OF PERITONITIS

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Original Submission:
03 April 2022
Revised Submission:
21 April 2022
Accepted:
04 May 2022

How to cite this article:
Delibegović S. 2022. Pathophysiology of peritonitis. Veterinaria, 71(2), 133-152.

ABSTRACT

Peritonitis signifies inflammation of peritoneum, whose cause is not specific. It can be regarded as local equivalent of systemic inflammatory response which is seen after any trigger of inflammation and referred to as systemic inflammatory response syndrome (SIRS). Peritonitis takes place together with many, complex pathophysiological changes on systemic and cellular level.

Keywords: Adhesion, cytokine, peritonitis, PMN

Physiology of the peritoneal cavity

The peritoneum is a smooth, transparent, serous membrane that coats the abdominal cavity as the parietal peritoneum, and coats the intraabdominal organs as the visceral peritoneum. This cavity is the largest extravascular space in the body, and the total area of the peritoneum is approximately equal to the body surface area in adults and is about 1.8 m^2. The functional area is smaller than the anatomical one, about 1 m^2, probably due to variations in blood supply (Delibegovic, 2007).

There is 50-100 ml of clear, sterile serous fluid in the peritoneal cavity. It is a plasma ultrafiltrate with electrolytes and a concentration similar to the adjacent interstitial space, and contains less than 30 g/l proteins, mainly albumin. Peritoneal fluid contains a small number of desquamated mesothelial cells and a variable number of morphologically different migrating immune cells (<300 cells/µl more than half of the normal cells are resident peritoneal macrophages, 44% lymphocytes, 2% dendritic cells, and a small number of eosinophils and fat cells) (Maddaus et al., 1988). Bacteria are absent because peritoneal fluid has minimal antibacterial activity due to the presence of complement. Under normal circumstances, the presence of this small amount of peritoneal fluid facilitates the mobility of the structures covered by the peritoneum. It is secreted by peritoneal serosa and absorbed, primarily, through the diaphragm. It is mainly resorbed through terminal lymphatic lacunae lying below the fissures (stomata, 10 to 16 µm in size, first described by von Recklinghausen in 1863) in the mesothelium, below the surfaces of the diaphragm, and is further drained into the larger mediastinal lymph vessels (Nakatani et al., 1996). Diaphragmatic lymph vessels allow the particles to leave the peritoneal cavity. The opposite flow is prevented by unilateral valves within these lymphatic vessels (Heemken et al., 1997; Hall et al., 1998) (Figure 1).

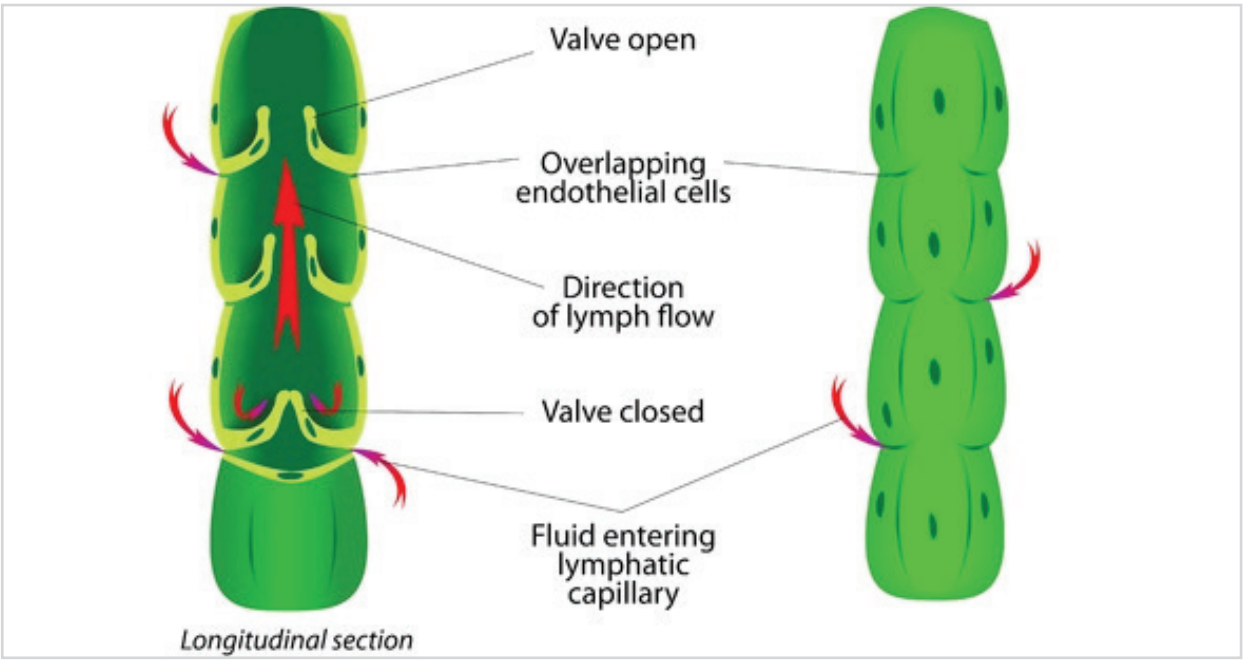

Figure 1 Longitudinal section of diaphragmatic lymph vessels.

Diaphragm movement, negative intrathoracic pressure, and positive intra-abdominal pressure move the peritoneal fluid and particles upward (Figure 2). Transport is fast and efficient. Thus, in humans, 1.0 to 3.0/l of fluid is transported daily through the left thoracic duct, which is a capacity of about 0.5 to 1.0 mg/kg/h. The total transport is probably even higher as a significant amount of fluid is also transported through the right ductus lymphaticus. This clearance mechanism is important for understanding the pathophysiology of peritonitis. It explains the early systemic manifestations of peritonitis. Soon after intestinal perforation, bacteria and their products are transported into the systemic circulation. Intraperitoneally administered drugs reach the systemic circulation in the same way. In contrast, intravenously administered antibiotics are rapidly found in the peritoneal cavity (Al Shoyaib et al., 2019).

Numerous factors can affect this diaphragmatic clearance. In animal models, blocking of this mechanism was achieved by the application of talc platelets. It has been observed that reducing breath intake, using general anesthesia, reduces this clearance. Even the application of PEEP (positive pressure at the end of expiration) reduces peritoneal bacterial clearance. Also, application of positive intrathoracic pressure worsens lymph flow.

Another clearance mechanism is phagocytosis by peritoneal macrophages (Dunn et al., 1985). These two effective mechanisms probably represent the "first line" of clearance after bacterial contamination. Peritoneal cavity sterility can be maintained despite many episodes of low bacterial inoculation, thanks to the efficacy of these local clearance mechanisms. However, if these mechanisms do not perform their function, an inflammatory response with further bacterial clearance follows, in order to localize or stop the infection. As a biological membrane, the peritoneum transports wa-

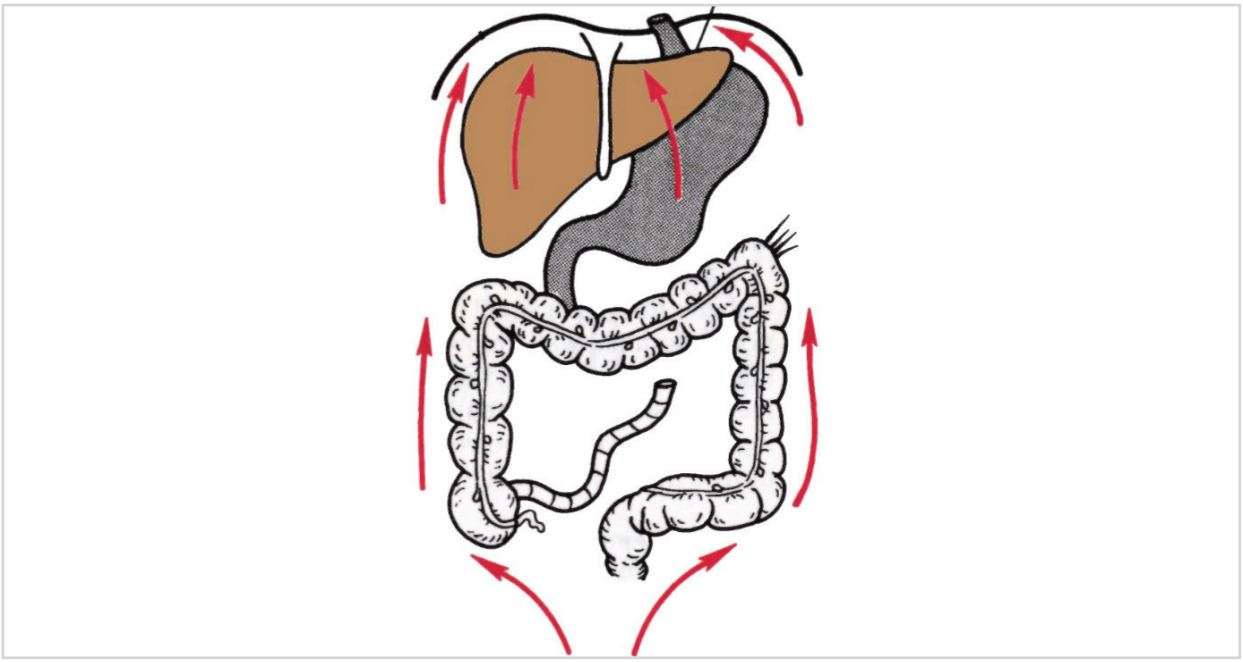

Figure 2 Peritoneal fluid flow.

ter, electrolytes, small molecules, and some macromolecules. Of the total area of the peritoneum, the functionally absorbable area is about 50%. Electrolytes, proteins and other endogenous and exogenous substances are freely absorbed. Factors thought to affect absorption include intraabdominal pressure, fever, dehydration, shock, increased portal pressure, lymphatic blockage, and a thick, scarred peritoneum. Isotonic saline, administered intraperitoneally after initial equilibrium, is absorbed at a rate of approximately 30.0-35.0 ml per hour. However, if a hypertonic saline solution is used, there is a large displacement of water (up to 300-500 ml per hour) from the intravascular space into the peritoneal cavity, which can result in hypotension and shock (Samson and Pasternak, 1979). This movement of water can be enhanced by agents that increase the blood flow or vascular permeability. Peritonitis has similar effects, and can cause rapid displacement from the intravascular and interstitial space into the peritoneal cavity, which can cause severe hypotension.

The movement of fluid through the peritoneum is two-way, between the peritoneal cavity and the plasma. For electrolytes, such as sodium and potassium, transport across the membrane takes place by diffusion. Transcapillary transport of macromolecules also takes place through the peritoneum, but it is not certain whether this is through intracellular fissures in postcapillary arterioles or through intracellular vesicles. Studies in humans and animals show that intraperitoneal blood is absorbed at a slower rate, but approximately 70% enters the blood-stream. This absorption occurs primarily through the fenestration of the lymphatic channels below the surface of the diaphragm. Such erythrocytes have a normal survival time in the circulation. Air and gas are similarly absorbed. The air that enters the peritoneal cavity during laparotomy is absorbed in 3-6 days (Makki, 2017).

Bacteriology of intra-abdominal infection

The infectious flora that leads to peritonitis usually consists of polymicrobial, polyaerobic and polyanaerobic flora. Cultures of intraperitoneal infection demonstrate up to five microorganisms per patient, although most clinical laboratories detect two to three per patient. Gram peritoneal exudate tests usually reveal pleomorphic Gram-positive and Gram-negative bacteria.

The gastrointestinal tract is a huge reservoir of bacteria, so much so that their amount is estimated at 1012 to 1014 in 1 ml of intestinal contents (Sender et al., 2016). They are not evenly distributed in the gastrointestinal tract. In the upper parts of the tract there is only 4% of the total number of bacteria, and in the colon as much as 96%. The oral cavity, esophagus and stomach are populated predominantly by Streptococci and Diplococci in an amount less than 1.000 bacteria per 1 ml. The acidic environment of the stomach is not conducive to the development of bacteria. However, in patients with achloridia, gastric cancer, and patients who are on mechanical respiratory ventilation and, at the same time, high doses of H_2 blockers, the amount of bacteria is higher and amounts to 100.000 to 1.000.000 in 1 ml. The dudodenum and jejunum contain a bacterial flora consisting mainly of Streptococci and Lactobacilli in quantities of 100 to 10.000 in 1 ml. The smaller the distance from the ileocecal valve, the higher the number of bacteria in the small intestine, so that the quantity of *Streptococci* and *Lactobacillus* increases to 1.000.000 to 10.000.000 in 1 ml.

The largest amount of pathogenic bacterial flora is in the colon. Of the huge number of bacteria, the most common are anaerobic bacteria, at over 95%. The most common of these are *Streptococcus, Bacillus species, Enteroccocci, Bifidobacteria,* and *Clostridiae.* In addition to bacteria, the colon also contains fungi of the genus *Candida* (Thursby and Juge, 2017).

Under normal circumstances, there are between 500 and 600 different bacterial species in the gastrointestinal tract that are in a complex symbiotic, saprophytic and parasitic relationship both with each other and with the host. The stability of the gastrointestinal flora is maintained by a number of factors, including competition for nutrients and mucosal binding sites, intestinal mobility, local pH, bile flow, and the production of antimicrobial substances by intestinal epithelium and other luminal organisms. If they leave their natural habitat and move to the peritoneal cavity, there is a drastic change in these complex relationships, so that many of the existing bacterial species, due to the loss of environmental conditions (intestinal lumen), do not survive in the new conditions. By moving into the intraperitoneal space, bacteria face the factors involved in the nonspecific defense of the organism, so that a large number of bacteria are destroyed in contact with macrophages. This process leads to the harmful selection of resistant pathogenic bacteria which, freed from natural competition, continue their uncontrolled growth and reproduction. These relationships result in the increased virulence of strains, and the full development of the inflammatory process. Thus, bacteria, which were not dominant in the intestinal lumen until then, begin to multiply rapidly and thus become the main carriers of the bacterial invasion. Therefore, a relatively small number of bacteria cause surgical infection, and only a few peritonitis. This explains the fact that the most common causes of intraabdominal infections are isolated strains of bacteria that are not present in large numbers in the normal intestinal flora (Table 1).

The character of the inflammatory process that takes place in the abdomen is conditioned, in the first place, by the type of bacteria that cause it. Another important feature is the amount of bacteria and their virulence (Wilson et al., 2002). Also, the pathological synergism of bacteria is important. It has been proven that severe forms of peritonitis only develop in the presence of mixed aerobic and anaerobic flora that determine the type and character of the disease.

Table 1 Bacterial cultures in patients with polymicrobial peritonitis

Aerobic bacteria	
Gram-negative bacteria	
Escherichia coli	60%
Enterobacter/Klepsiella	26%
Proteus	22%
Pseudomonas	8%
Gram-positive bacteria	
Streptococci	28%
Enterococcus	17%
Staphylococci	7%
Anaerobic bacteria	
Bacteroides	72%
Eubacteria	24%

Adjuvants

Many experiments have shown that certain substances, referred to as adjuvants, alleviate infection. These are sterile stool, barium sulphate, bile, mucus or hemoglobin. Bile, in itself, is not toxic, but it reduces surface tension and facilitates the spread of bacteria. Mucus inhibits phagocytosis by enveloping bacteria. The adjuvants' role in the lethality of experimental peritonitis has also been attributed to the presence of large amounts of fluid within the peritoneal cavity (Dunn et al., 1984). Fluid left after rinsing, during laparotomy, or due to ascites, may delay bacterial clearance, enhance bacterial growth, or reduce phagocytosis by diluting intraperitoneal opsonins.

Peritoneal response to infection

Intraabdominal infection results from perforation of hollow organs leading to inoculation of bacteria into a normally sterile peritoneal cavity (Figure 5). The normal bacterial flora found at a specific location in the gastrointestinal tract, determines the initial inoculum. Some studies suggest that the quantity of bacteria present at the onset of intra-abdominal infection is higher than previously thought (approximately 2 x 108CFU/ml, much more than the routinely used 5 x 105CFU/ml inoculum for in vitro testing). The exact events that follow the inoculation of the peritoneal cavity with bacteria and adjuvants of infection (blood, bile, barium sulfate), and the consequent translymphatic systemic spread are the subject of further research. In animal models, when bacteria are injected into the peritoneal cavity, they disappear even before polymorphonuclear leukocyte (PMN) influx, and can be found in diaphragmatic lymph vessels within 6 hours after injection (Hall et al., 1998). This suggests that one of the most important defense mechanisms of the peritoneal cavity is the direct absorption of bacteria into the diaphragmatic lymph vessels, and the consequent exposure of bacteria to systemic defense mechanisms such as tissue macrophages, reticuloendothelial cells and PMN. During the initial phase of infection, resident macrophages and, probably, fat cells, in cooperation with the clearance mechanism, act as the first line of peritoneal defense to reduce the number of bacteria. This interaction between bacteria and resident macrophages serves to increase the local defense response, with the release of proinflammatory mediators that attract and inform other cells, such as PMN. After the first few hours, there is an influx of PMN into the peritoneal cavity in response to the chemotoxic stimuli released by tissue macrophages, bacterial products such as N-formyl peptides, and complement activation. These cells destroy the microorganisms that have penetrated and escaped other defense mechanisms. The pro-cess lasts for several hours and clearly coincides with the critical period during which the interaction occurs between bacterial proliferation and the host defense mechanisms aimed at destroying pathogenic microorganisms. Chemotaxis is an important initial step, but many microorganisms, especially encapsulated ones, must be opsonated with a sufficient amount of specific antibodies to be ingested. Activated C3 and IgG are the most important opsonins.

Macrophages are pluripotent cells that play a central role in coordinating the overall inflammatory response. They secrete proinflammatory cytoki-nes, such as tumor necrosis factor (TFN-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), which enhance the microbicidal properties of other phagocytic cells within the surrounding milieu, and attract additional phagocytic cells to the site of invasion and infections (Lopez et al., 2011). Macrophages also act as cells that process and represent components of the pathogen to T-helper cells, resulting in activation of the adaptive immune response. The final route of all these events

is the killing of bacteria, the elimination of foreign materials and the reestablishment of normal physiology and anatomy. Bacterial killing or cytotoxicity can be achieved through oxygen free radicals, nitric oxide, cytotoxic lymphocytes, proteins that increase bacterial permeability, cathepepsin, lactoferrin, lysosomes, proteases, lipid hydrolases and kinases.

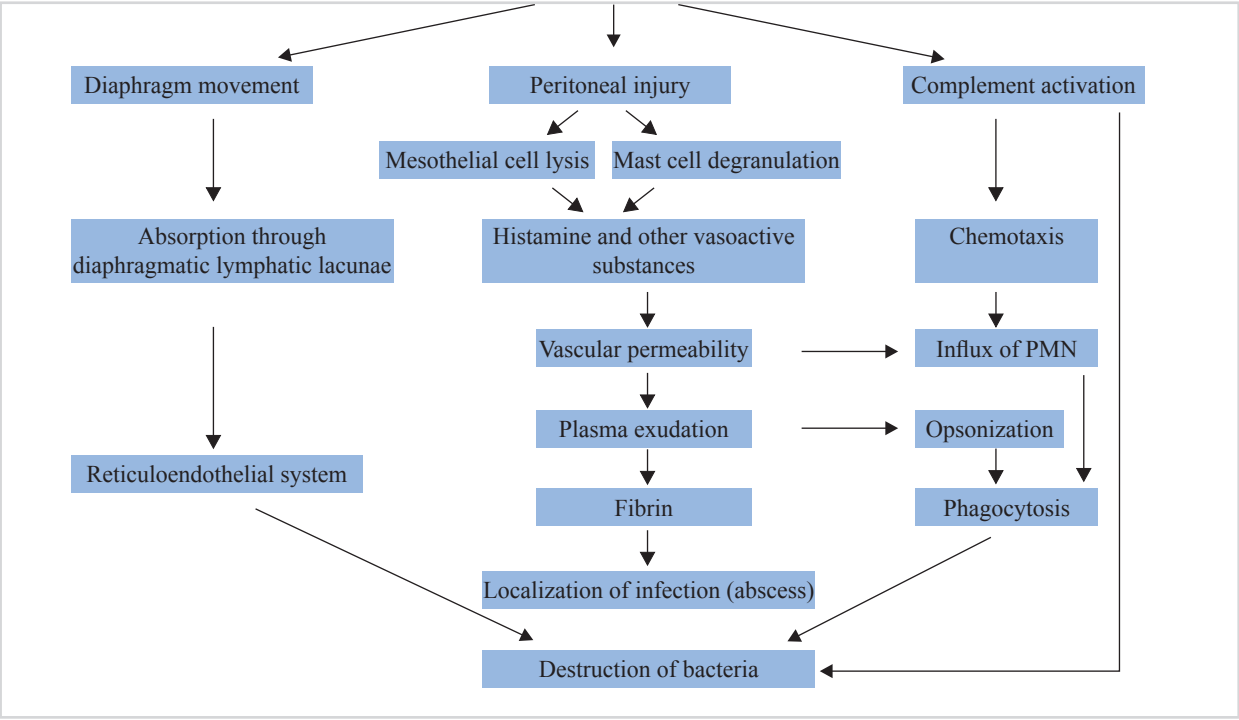

Figure 3 Pathogenesis of secondary peritonitis.

There are, however, quantitative limitations to each of these mechanisms in dealing with contamination. Those microorganisms that avoid clearance and phagocytosis are opposed by a final, primitive defense mechanism (sequestration) that protects the host from bacterial inoculum. The expression of tissue factor on the surface of peritoneal macrophages initiates local activation of the coagulation cascade, which results in fibrin deposits around the inflammatory focus (Weiss and Schaible, 2015). This process serves to limit infection from the rest of the peritoneal cavity. By acting together with the omentum and other mobile organs, the perforation is closed and, as the ileus develops, the contaminated intestinal contents are surrounded and the continuation of contamination of the peritoneal cavity is prevented. Fibrin itself has the ability to trap a large number of bacteria and also to boost the immune response. Fibrin exudate production is considered to be an important part of host defense, but a large number of bacteria can be sequestered within the fibrin matrix that are thus protected from the action of the host clearance mechanism. This can reduce the spread and systemic dissemination, and reduce early mortality from sepsis, but this is also a pathway for the development of residual infection and the formation of abscesses (Ordonez and Pouyana, 2006).

The anatomy of the peritoneum explains some of the early pathophysiological changes seen in intra-abdominal infection. Histamine and other vasoactive substances, released during the host's defensive reaction, increase the vascular permeability of the peritoneum. Transudation of low-protein fluid from the extracellular interstitial compartment into the peritoneal cavity was accompanied by the diapedesis of a large number of PMNs. During the early vascular and transudative phases, the peritoneum is a "two-way street", so that toxins and other substances, which may be in the peritoneal fluid, are easily absorbed, enter the lymphatic and bloodstream, leading to systemic symptoms. Transudation of interstitial fluid into the peritoneal cavity, through the inflamed peritoneum, is accompanied by exudation of protein-rich fluid. This exudate contains large amounts of fibrinogen and other plasma proteins in a con-centration sufficient to lead to coagulation, so that adhesions form between the intestinal villi and other organs in the area of peritoneal inflammation.

After perforation and the entry of bacteria into the peritoneal cavity, the massive inflammatory response includes vasodilation and exudation of fluid, and up to 10.l of fluid can move into the peritoneal cavity and subendothelial connective tissue (Ordonez and Pouyana, 2006). It has been estimated that a 1 mm thick peritoneum can sequester up to 18.l of fluid, which clearly shows how large the fluid displacement can be in diffuse peritonitis. Atonic, dilated intestines also accumulate fluid in their lumen. Depending on the severity of the infection, the formation of inflammatory peritoneal edema may occur so rapidly that it manifests clinically as hypovolemic shock. Continuous accumulation of fluid in the peritoneal cavity may also exacerbate bacterial phagocytosis by diluting opsonin and reducing neutrophil mobility and migration. At the same time, gravity causes the reverse flow of fluid, so the inflamed exudate in the peritoneal cavity goes downward (Figure 4).

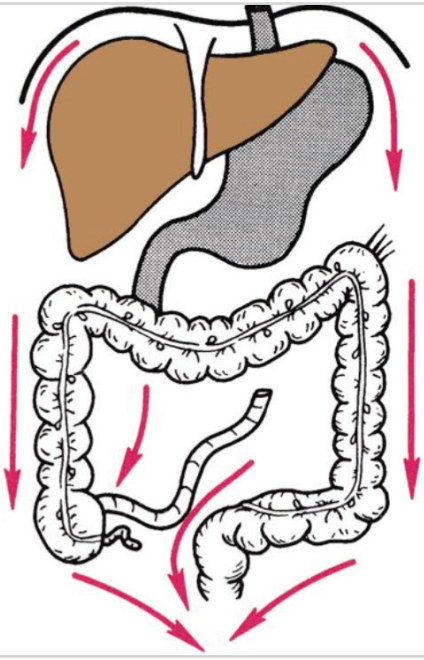

Figure 4 Peritoneal fluid flow in infection.

Exudate basins are formed in the lower parts of the peritoneal cavity, such as the subphrenic spaces and pelvis (Petermann, 1927) (Figure 5). Clinical observation suggests that mortality in peritonitis is reduced in patients who are placed in a semi-sitting position, which is probably associated with a decrease in bacterial absorption through the diaphragm (Figure 5).

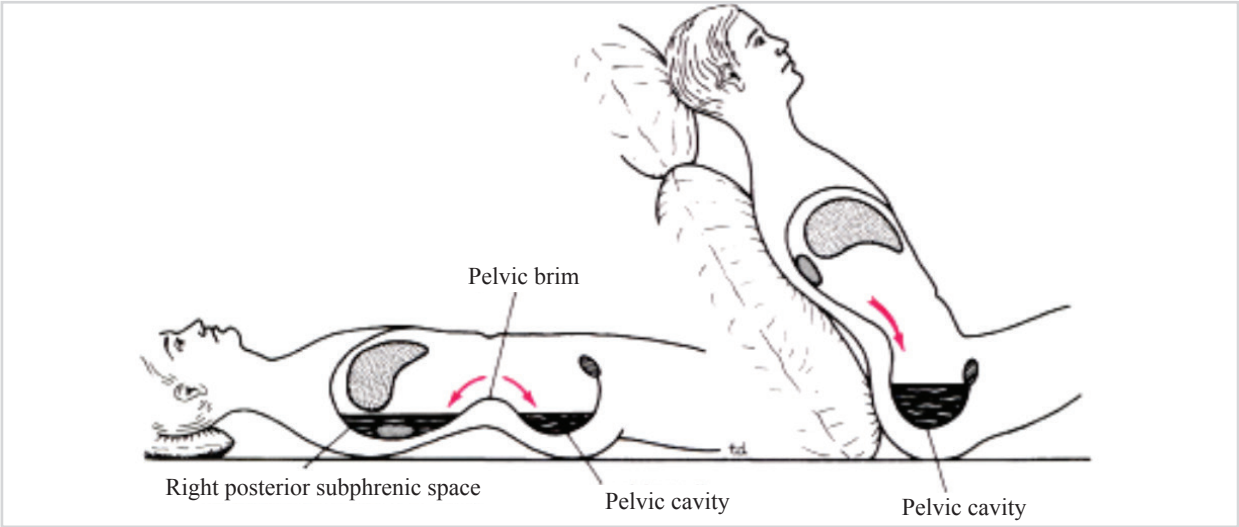

Figure 5 The influence of a semi-sitting position on absorption.

At the same time, the parietal peritoneum in the pelvis is thought to be more resistant to infection, due to the smaller number of lymphatic lacunae are closed by cell debris and fibrin patches.

The acute inflammatory process within the abdomen results in sympathetic activation and suppression of intestinal peristalsis. Fluid absorption through the intestinal wall is impaired and a significant amount of tissue fluid can be sequestered within the intestine. Reduced intestinal peristalsis stimulates the growth of bacteria, and leads to the translocation of bacteria and their products from the intestinal lumen to regional lymph nodes, peritoneal cavity and portal circulation. Blood shunt from the splanchnic circulation in response to the relative hypovolemia, sequestration of fluid in the third space, and peripheral vasodilation in response to inflammatory stimuli further compromise intestinal barrier function and affect bacterial translocation and absorption of endotoxins from the intestinal lumen.

Sequestration of fluid within the peritoneum and peritoneal cavity, as well as within the intestinal lumen, significantly increases intra-abdominal pressure, and can cause abdominal compartment syndrome (Hold and Agnello, 2014). Increased intra-abdominal pressure negatively affects pulmonary, cardiac and renal function, but also hepatic planar perfusion. It may be accompanied by an increase in intrathoracic pressure, due to respiratory therapy or inhalation anesthesia. In combination with PEEP, this results in a significant increase in central venous pressure, pulmonary capillary wedge pressure, mean pulmonary arterial pressure and pulmonary vascular resistance, and decreased venous blood return to the heart, with changes in ventricular compliance, all accompanied by hormonal depression of cardiac function.

The course of the infection

Regardless of the mechanism of peritonitis, it goes through all the classic stages of inflammation. The primary reaction of the peritoneum to the agent begins with lysis of mesothelial cells and degranulation of mast cells (Figure 5). Those in the damage zone release large amounts of proinflammatory mediators into the interstitial space. Activation of resident macrophages occurs, and positive chemotaxis causes the transition of PMN to the zone of inflammation. The local effect of vasoactive substances is reflected in the vasodilation and increased permeability of the small peritoneal blood vessels. In parallel with this process, the complement system is activated. Due to the action of the toxin, blood vessels are paralyzed with consequent dilatation, creating a pathway and the exudation of fluid. These defense mechanisms will cause phagocytosis of the bacteria, which successfully defends the organism from bacterial infection.

If the local defense mechanisms are insufficient to suppress the bacterial infection, the inflammatory process continues and expands, and fibrinogen passes into the zone of inflammation or into the free peritoneal cavity (Broche and Tellado, 2001). The coagulation cascade, activated in the peritoneal cavity, results in the formation of thrombin, which triggers the conversion of fibrinogen to fibrin (Pattinson et al., 1981). Fibrin deposits are initially useful because they localize the intraperitoneal infection. However, a large number of bacteria can be sequestered within the fibrin matrix, and are thus protected from the action of the host clearance mechanism. This represents a way in which abscesses are created in experimental models (Broche and Tellado, 2001).

Along with the transfer of fibrinogen from the blood vessels, PMNs occupy a peripheral arrangement in the blood vessels and begin mass migration into the peritoneal cavity. This leads to the formation of pus. The pus consists of necrotic and damaged PMN, inflammatory cells, cellular detritus, causative microorganisms, and transuded fluid. Regardless of the degree and type of inflammatory process that takes place in the peritoneal cavity, further propagation of the infectious process is possible. Lymphatic openings of the peritoneum resorb large amounts of exudates, but also bacterial cells. If the macrophages do not phagocytose penetrating bacteria, there is a possibility of bacteria passing into the general circulation, and peritonitis is complicated by sepsis, septic shock, and the consequent development of multiple organic dysfunction/insufficiency syndrome (Figure 6).

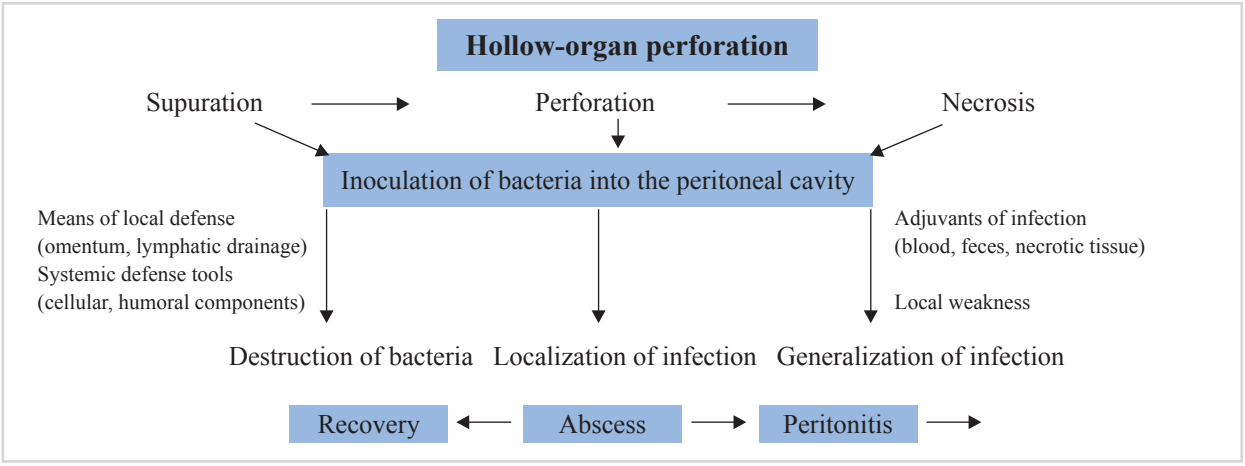

Figure 6 Pathogenesis of secondary peritonitis.

Adhesions

The peritoneum heals very soon after injury. Unlike the skin, which is completely contracted by the wound and the centripetal growth of new epithelium from the edges of the wound, a peritoneal defect is renewed at the same time everywhere. A very large defect can heal at the same rate as a small defect. It has been experimentally proven that 3 days after a peritoneal injury, the damaged surface is covered with a layer of connective tissue cells that look like mesothelial cells. On the fifth day, the new surface layer looks like a normal mesothelium. On the seventh day, mesothelial regeneration is complete. The exact origin of these cells, responsible for mesothelial regeneration, remains unclear. Evidence supports a bimodal mechanism involving the migration of mesothelial cells to the edge of the defect, and the implantation of free, floating peritoneal mesothelial cells (PMCs) on the wound surface. It is also possible that pluripotent cells below the mesothelium migrate to the surface and differentiate into PMC. Macrophages play an important role in mesothelial healing by inducing PMC proliferation (Herrick and Wilm, 2021).

The metabolic changes in the inflamed peritoneum are similar to those that occur in dermal inflammation, but they appear much faster. The synthesis of membrane glycoproteins and proteoglycans is increased. The concentration of uronic acid is also increased, probably reflecting the exudation of plasma proteins in the early stages of peritonitis, and in the later stages the synthesis of glycoaminoglycans is increased due to the activation of fibroblasts and mesothelial cells. Experimental studies of peritoneal metabolism in peritonitis show increased oxygen and glucose consumption and increased lactate production. There is also an increase in anaerobic metabolism, mainly due to glycolysis. Together with a decrease in partial pressure and increased oxygen consumption, these changes lead to a hypoxic environment in the peritoneal cavity, which encourages the formation of adhesions and the growth of anaerobic bacteria.

A normal peritoneal wound heals smoothly, without the formation of adhesions. Adhesions develop in response to factors other than simple peritoneal healing. Local tissue hypoxia and wound ischemia are important factors in adhesion stimulation (Nauta et al., 2014). Other causes are mechanical damage to the subperitoneal surface and contamination of the peritoneal surface with foreign materials.

Pathophysiology of intraabdominal adhesions

Peritoneal trauma results in mesothelial damage accompanied by inflammation (Herrick and Wilm, 2021). Mesothelial cells enlarge and separate from the basement membrane, creating denuded regions. The inflammatory response is accompanied by the production and release of a wide range of biologically active proteins and the exudation of a proteinrich fluid. Peritoneal exudate contains large amounts of fibrinogen. The coagulation cascade, activated in the peritoneal cavity, results in the formation of thrombin which triggers the conversion of fibrinogen to fibrin. By activating the fibrinolytic system, any intra-abdominal deposit can be lysed. Under normal conditions, there is a balance between fibrinolysis and coagulation.

Surgery, extensive and severe peritoneal injuries, intraabdominal infection, tissue ischemia, hypoxia, or intraperitoneal foreign bodies disturb this balance in favor of the coagulation system. Fibrin forms deposits that are a matrix for the growth of fibrocollagen tissue. Fibroblasts and capillaries grow into arachnoid fibrin adhesions, followed by collagen deposits, which results in fibrous adhesions. In addition, fibrin deposits protect bacteria from the immune defenses of the peritoneal cavity.

Activation of the fibrinolytic system results in the conversion of plasminogen to plasmin. Plasmin is highly effective in creating fibrin degradation products. Plasminogen is present in high concentrations, and only small amounts of plasminogen activator are required to produce large amounts of plasmin. The plasminogen activators are tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). tPA is a major plasminogen activator and has a high affinity for fibrin. In the peritoneal cavity, it is responsible for 95% of plasminogen activation. Various cells produce tPA, including endothelial cells, mesothelial cells, and mac-rophages. Plasminogenic activity is prevented by plasminogen activator inhibitors, types 1 and 2 (PA-1, PA-2). PA-1 is a major inhibitor of tPA and uPA, and is produced by a variety of cells, including endothelial cells, mesothelial cells, macrophages, and fibroblasts. PA-2 probably plays a role in peritoneal repair (Sulaiman et al., 2002).

Surgery and infection in the peritoneal cavity disturb the balance between coagulation and fibrinolysis. In peritoneal fluid, fibrinolytic activity is reduced mainly due to the increase in PA-1. Therefore, PA-1 is considered an important factor in the development of adhesions. It is also of great importance that PMCs have a predilection to grow within blood clots, emphasizing the potent role of blood clots in adhesion formation. This explains why adhesions are thickest when two denuded surfaces are joined to coagulated blood. Adhesion formation is a protective mechanism that helps localize peritoneal stroke, but also an adaptive response that helps bring additional blood supply to the ischemic injured region of the peritoneum.

Adhesion prevention

Prevention of the formation of adhesions after surgery focuses on minimizing peritoneal trauma and reducing the introduction of foreign materials into the peritoneal cavity, as they can enhance the inflammatory response (Gonzales-Quintero and Cruz-Pachano, 2009). Activation of the fibrinolytic system is also considered. The effect of tPA as the major plasminogen activator has been studied and, although it has shown efficacy, the risk of bleeding has been a major barrier to routine use. Antiinflammatory drugs, including corticosteroids and prostaglandin synthetase inhibitors, have also been tested. A promising concept may be the intraperitoneal application of hyaluronic acid, which prevents the formation of adhesions (Vrijland et al., 2002).

Inflammatory response in peritonitis

Any agent, such as a bacterial endo- or exotoxin, can initiate a series of events known as the inflammatory response (Dickinson and Lehmann, 2019). Although an adequate inflammatory response provides an essential defense against infection, a reduced or excessive response can lead to significant morbidity and even mortality. The inflammatory response is the end product of the complex interaction between cellular and humoral components (Figure 7). The humoral components are molecules that circulate in the body, including antibodies and the complement system, quinines, lipid mediators, and acute phase cytokines.

Cellular components consist of granulocytes, mononuclear phagocytes, lymphocytes and various non-leukocyte cells that affect many processes during inflammation. Microscopically, these cellular and humoral elements lead to changes in the local vascular network mediated by quinines, cytokines, chemokines, lipid mediators, neuropeptides, reactive oxygen species, and nitrogen products. Within 30 to 60 minutes, neutrophils marginalize, extravasate, and accumulate at the site of inflammation, where they ingest pathogenic microorganisms and release oxidants and proteases (Rosales, 2018).

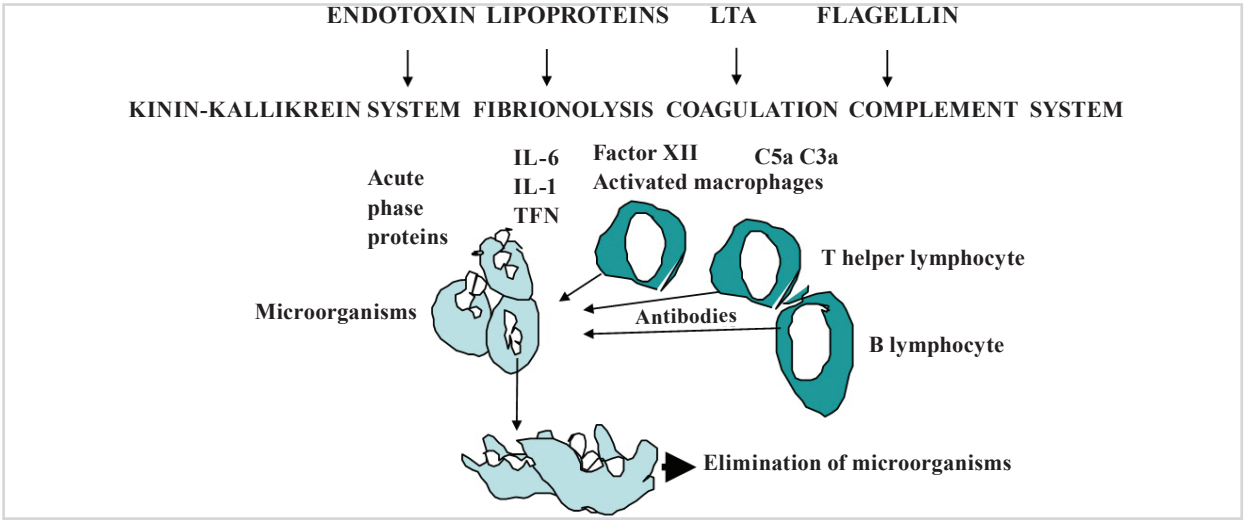

Figure 7 Inflammatory response in peritonitis.

Within 4 to 5 hours, mononuclear cells (monocytes and lymphocytes) begin to accumulate at the site of inflammation. The attracted monocytes and resident macrophages participate in nonspecific phagocytic activity, while lymphocytes initiate specific, antibody-dependent cell lysis.

Cellular components

A large number of different cells on several levels serve as the host's defense. As already mentioned, during the initial phase of infection, macrophage residents act as the first line of peritoneal defense against infection and participate in the initial clearance of pathogenic microorganisms through phagocytosis. Macrophages also act as antigen-processing cells and present them to the T-helper cells, thus initiating an immune response.

Macrophages are pluripotent cells that play a central role in coordinating the overall inflam-matory response. Through their interaction with microorganisms, these cells are activated, with the creation of a wide range of mediator molecules capable of numerous immune functions. Thus, for example, polymorphonuclear leukocytes (PMNs), cells with high microbicidal capacity, are found within the bloodstream but in small numbers in tissues. They are mobilized to the extravascular site of infection via diapedesis in response to the chemotactic stimuli released by tissue macrophages, bacterial breakdown products such as N-formyl peptides, and complement activation. This process lasts for several hours and coincides with the critical period during which the interplay of bacterial proliferation and reduction of infection due to the host response occurs (Durum and Rotstein, 2001).

Local activation of defense mechanisms can also have a detrimental effect on the host. Secretion of lysosomal enzymes (cathepsin, elastase), free radicals (superoxides, hydroxyl), nitric oxide and cytokines secreted by macrophages and PMN can damage neighboring cells, but also lead to tissue damage far from the site of infection. Systemic activation of the inflammatory response can induce excessive activation of circulating immune cells, as well as those in distant organs, resulting in organ damage and the development of multiple organic dysfunction/insufficiency syndrome (MODS/MOF).

Early response cytokines

Cytokines are low molecular weight polypeptides secreted after initial activation of macrophages or lymphocytes, and may themselves act on the cells that secrete them (autocrine activation), or on other cells within the same milieu (paracrine stimulation), and increase the secretion of the same or other cytokines. They have a wide range of actions at both the local and systemic levels. They play an important role in regulating the immune response, and act in different ways on T and B cells, monocyte-macrophage line cells, neutrophils, fibroblasts, smooth muscle cells, endothelial and epithelial cells. Immune functions affected by these polypeptides include the host's response to acute and chronic bacterial, viral, fungal, parasitic infection, trauma, burns, allograft rejection, ischemicreperfusion injury, and autoimmune diseases. They play an important role in tumor biology and angiogenesis. Excessive cytokine release is responsible for the development of acute respiratory distress syndrome (ARDS) and MOF. Their various actions and effects are numerous. The most important cytokines are tumor necrosis factor-α (TFN-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) (Moshage, 1997, Sakashita et al., 2000).

Table 2 Effects of early response cytokines

Source	Monocytes/ macrophages, keratinocytes, Kupffer cells, fibroblasts, astrocytes, glial cells, fat cells, NK cells, T and B lymphocytes	Monocytes/macrophages, keratinocytes, Kupffer cells, fibroblasts, endothelial cells, astrocytes, microglial cells, epithelial cells, PMN, vascular smooth muscle cells, epithelial cells, NK cells, T and B lymphocytes	Monocytes/ macrophages, keratinocytes, Kupffer cells, fibroblasts, endothelial cells, astrocytes, PMN, microglial cells, T and B lymphocytes, epithelial cells.
Rise in body temperature	++	+++	+
Shock induction	+++	++	+/-
Stimulation of the acute phase of the response	+	++	+++
Endothelial cell activation	+++	++	+/-
Procoagulant activity	+++	++	+/-
Anorexia, weight loss	+++	++	+/-
Fibroblast proliferation	++	++	-

NK - natural killer cells

Anti-inflammatory cytokines

Although generally considered proinflammatory, cytokines may also have antiinflammatory effects, and are important in regulating the overall inflammatory response. The main anti-inflammatory cytokines are IL-4, IL-10, IL-13 and TGF-γ (Badiu et al., 2011). These molecules were discovered due to their ability to inhibit the production of TFN-α in LPS-stimulated macrophages. Blockade of any of these leukins increases TFN-α levels and attracts neutrophils. The IL-1 receptor antagonist (IL-1ra) is a product of stimulated macrophages and also a counterregula-tory factor in the inflammatory response. These cytokines antagonize proinflammatory effects by increasing IL-1ra and soluble TFN receptors. IL-4, IL-10, IL-13 are produced by the Th2 subclass of helper T cells and share many similar effects. The procoagulant state of inflammation is reduced by their inhibition of LPS-induced tissue factor activity. IL-4, IL-10, IL-13 inhibit the induction of COX-2 and iNOS in monocytes and macrophages.

Interleukin-10 appears to be the most potent anti-inflammatory cytokine in this group (Kato et al., 1995). It is secreted predominantly by monocytes and macrophages, and by T and B lymphocytes. IL-10 production is increased by exposure to LPS, TFN-α, IL-4, IL-13. IL-10 reduces the syn-thesis of TFN-α, IL-1, IL-6 and IL-8 in monocytes and macrophages. IL-10 also stimulates the release of other anti-inflammatory molecules, specifically soluble TFN-α receptors and IL-1ra. Serum IL-10 levels are often elevated in burns, injuries, sepsis, ARDS and MOF. According to some studies, patients with the highest levels of IL-10 died (Emparan and Senninger, 2000). It is unclear whether this is a pathological response or a marker of the severity of the damage. The IL-10 molecule may be important in the development of inflammatory bowel diseases, such as ulcerative colitis or Crohn's disease. Preliminary clinical findings show the benefits of IL-10 therapy, suggesting that these diseases may be the result of a disturbed balance of proinflammatory and antiinflammatory cytokines.

Interferons

Interferons are unique because they possess potent antiviral and antitumor properties. They are divided into type I (IFN-α, INF-β) and type II (IFN-γ) interferon (Weighardt et al., 2006). Type I interferon can be produced by any cell when properly stimulated. Viruses are the most potent inducers of IFN-α and INF-β (Nagarajan, 2011), but also LPS, double-stranded RNA, IL-1 and TFN-α. IFN-α, and INF-β regulate the expression of MHC class I molecules. They also stimulate B cell development and the proliferation and change of IgM immunoglobulin heavy chains to IgG. Type I interferon inhibits cell replication of normal and tumor cells, and enhances NK cell activity. Type II interferon is only produced by T cells and activated NK cells. IFN-γ is a major activating factor for macrophages. It regulates the expression of MHC class II and class I molecules. It is involved in reciprocal stimulation with TFN and IL-12. Stimulated macrophages activate NK cells by releasing TFN and IL-12, and these activated NK cells then release IFN-γ, which further stimulates macrophages to secrete more TFN and IL-12. IL-12 released from monocytes and macrophages activates Th1 cells while inhibiting the TH2 subclass. IFN-γ induces the release of IL-1 and IL-6 and, together with TFN and IL-6, may act synergistically to mediate cytotoxicity. IFN-γ stimulates the attraction of inflammatory cells and enhances microbicidal activity in macrophages and neutrophils.

During the initial activation of macrophages, in response to bacterial products, interferon-γ (IFN-γ) is released by T cells and IL-1 by macrophages (Ivashkiv, 2018). The secretion of IFN-γ and IL-1

may be accompanied by the secretion of TFN-α by macrophages, followed by the secretion of IL-6 and other cytokines. In experimental models, IL-1 is capable of producing fever, hypotension, while TFN-α causes fever, hypotension, intestinal ischemia, and death. Approximate-ly 1.5 to 2 hours after lipopolysaccharide (LPS) administration, IL-1 and TFN-α are produced, followed by IL-6 and IL-8 secretion (Kumolosasi et al., 2014).

The duality of the effects of cytokines on the host itself is becoming more and more important. In experimental models, the application of TFN or IL-1 strengthens the host's defenses, but the initial application of high doses leads to death. As noted, excessive activation of local defenses may result in cytokine entry into the systemic circulation. This process is most likely to explain the occurrence of a "septic condition" or systemic inflammatory response syndrome (SIRS) in patients in whom no active infection can be identified.

Humoral components

Stimulation of the immune system occurs after different cells present processing antigens (macrophages, B lymphocytes, dendritic cells, Langerhans cells) to T-helper cells (Chaplin, 2010). These T lymphocytes stimulate B lymphocytes that become mature plasma cells with the production of antibodies directed against specific antigens. At the same time, complement cascade activation by certain antibodies occurs. However, many other substances are able to activate the complement cascade directly, in a classical or alternative way. Thus, for example, Gram-negative microorganisms are able to activate one or both pathways, while many fungi activate the alternative pathway directly. The complement cascade is a relatively primitive host de-fense mechanism that is extremely effective in preventing infection, especially when acting in conjunction with other components of the defense system.

Overall, antibodies and complement work together to neutralize microbial toxins, lyse pathogenic microorganisms, and/or significantly enhance phagocytosis of those microorganisms that have avoided initial neutralization and lysis. At the same time, fragments of some complement components attract additional cellular defense components and direct them toward the area of infection.

The coagulation cascade also plays an important role in the local and systemic inflammatory response (McGilvray and Rotsein, 1998). This process of immune coagulation is mediated by molecules on the cell surface, such as tissue factor, plasminogen activator and plasminogen activator inhibitors, which to some extent used to determine the balance between procoagulant response and anticoagulant/fibrinolytic activity. In general, infection and inflammation induce a procoagulant response by increasing molecules such as tissue factor and plasminogen activator inhibitors on monocytes/macrophages and endothelial cells and overall lead to decreased plasminogen activator activity. This insurance of fibrin deposits encourages local inflammation due to the potent immunomodulatory effects of its breakdown products. However, this can also contribute to damage to distant organs through the induction of microvascular thrombosis.

Integration of inflammatory components

The acute phase response is characterized by changes in liver metabolism, activation of the central nervous system, leading to fever and adaptive behavior, altered hematological profile, activation of the complement, fibrinolysis and coagulation cascades, and release of neuropeptides, quinine and hormones (Grys et al., 2005). It is a rapid, nonspecific response that occurs before a specific immune response. Cytokines are the main mediators of the acute phase response, and IL-6, IL-1 and TFN-α play a central role.

Acute phase proteins are proteins whose concentration increases by at least 25% during in-flammation. They begin to grow after a delay of approximately 6 hours, and serve to establish homeostasis after infection or inflammation. These include haemostatic functions (fibrinogen), microbicidal and phagocytic functions (comple-ment components, CRP), antithrombotic properties (α1-acid glycoprotein, plasminogen), antioxidant properties (haptoglobulin, hemopexin) and antiproteolytic properties, α1-α1-α2-α2-inhibitor protease and α2-antichymotrypsin). The size of the response depends on the severity of the stress and varies from patient to patient. Systemic manifestations include neuroendocrine changes, changes in hematological profile, and metabolic and chemical changes. The classic neuroendocrine man-ifestation is a rise in body temperature. IL-1, IL-6 and TFN mediate by acting on the hypothalamic center through PGE2 synthesis. Secretion of neuropeptides, such as arginine vasopressin (AVP), and corticotropin-releasing hormone (CRH), and hormones, such as glucagon, insulin, thyroxine, and aldosterone, is also characteristic in the acute phase of the response. CRH and AVP released in the hypothalamus increase ACTH and cortisol levels. An increase in cortisol levels is one of the earliest signs of systemic changes. The release of cortisol inhibits the rise in temperature and the gene expression of cytokines, contributing to its potential regulatory function in the acute phase of the response.

Glucocorticoids increase the synthesis of some acute phase proteins involved in connective tissue repair and coagulation (fibrinogen), as well as antioxidants and antiproteinases (haptoglobin and α2-macroglobulin) (Russo-Marie, 1999). They may also function as a counterbalance to the hypoglycaemic response due to excessive insulin production during infection or stress. In this way, glucocorticoids may act together with glucagon and epinephrine to increase blood glucose levels during the acute response phase. Metabolic changes include altered lipid status and negative nitrogen balance. Plasma levels of zinc and iron decrease, and copper levels increase. This decrease in zinc and iron levels is accompanied by a decrease in plasma binding proteins (transferrin and albumin). Low levels of these metals can have a protective effect, as they are essential for microbial growth. Bacterial products, such as LPS, are the most potent activators of the tissue macrophages that initiate the acute phase response. LPS, through interaction with the LPS binding protein, CD14 and Toll-like receptors, induces the synthesis of free radicals and reactive oxygen species including NO, lipid derivatives such as PGE2, thromboxane A2, FAT and acute phase cytokines.

Monitoring the inflammatory response

Many parameters change during an infection. These include cytokines, mainly secreted from monocytes (IL-1, IL-6, IL-8, IL-10, IL-18 and TFN-α), functional changes in granulocytes (chemotaxis, phagocytosis, oxygen radical form-ation), histamine release from fat cells, NO expression and adhesion of molecules to endothelial cells, release of coagulation factors, complement factors, adhesion of molecules and procalcitonin (PCT) from epithelial cells (Attia et al., 2012). These changes produce biological effects, such as fever, metabolic disorders, dilation of blood vessels, capillary permeability, and disseminated intravascular coagulation.

The biological effects lead, in severe cases, to the classical clinical indicators that are routinely mon-itored during infection, including: decreased car-diac output, hypotension, hypovolemia, intestinal edema, and multiple organ dysfunction.

Therapeutic decisions are based on monitoring the patient's inflammatory status. Common laboratory parameters, such as leukocyte count and C-reactive protein, are nonspecific to distinguish between bacterial and nonbacterial infection. They manifest late, when clinical signs are already evident.

Monitoring parameters

Of the potential markers, the highest predictive value for the development of sepsis is found in IL-6 and procalcitonin. SIRS generally correlates with an increase in PTC levels greater than 3 ng/ml, and IL-6 more than 98 pg/ml, while sepsis results in levels greater than 16 ng/ml for PTC and 380 pg/ml for IL-6. The easiest way to measure cytokines is to use peripheral venous blood. The assay is performed using a commercial immunoassay such as ELISA and RIA (Zhou et al., 2010).

Clinical factors that may alter the inflammatory response

Major surgery is associated with an increase in circulating TFN-α and IL-6 on the first day after surgery, and with a return to normal levels in the absence of infection the day after. In most cases, PCT does not increase after surgery, but it seems to be more specific for detecting infection. Anemia induces a decrease in the production of proinflammatory cytokines, which is further enhanced by blood transfusions, resulting in a worsened response to infection. Malnutrition is also associated with significant immunosuppression, characterized by atrophy of lymphoid organs, impaired cellular immunity, and an increased risk of viral and opportunistic infections. Hyper and hypoglycemia are associated with inhibition of IL-1 synthesis and release from macrophages. The kidneys play a role in cytokine metabolism and clearance. Cytokine expression and release are also altered by pharmacological interventions. Catecholamines, antimicrobials, analgesics, narcotics, histamine antagonists, anticoagulants, calcium channel blockers and various other drugs can affect the level of cytokines in the blood. Also, well-known risk factors for adverse surgery outcome, such as old age and trauma, gender and genetic predisposition, may modulate cytokine expression. It is necessary to think about these complex interactions when interpreting findings (Chen et al., 2018).

CONCLUSION

Host defense during peritonitis is extremely complex, due to the interaction that occurs between different forms of host defense. Two important issues need to be emphasized: a) while the individual host acts as a series of barriers to infection, many defense components can act in tandem and/or synergistically to prevent infection, b) many host defense components can have a destructive effect on the host; so that an excessive response alone can cause organ damage and the development of multiple organic dysfunction/insufficiency syndrome.

CONFLICT OF INTEREST

The author has no conflict of interest.

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PATOFIZIOLOGIJA PERITONITISA

SAŽETAK

Peritonitis označava upalu peritoneuma, čiji uzrok nije specifičan. Može se smatrati lokalnim ekvivalentom sistemskog upalnog odgovora koji se vidi nakon bilo kojeg pokretača upale i naziva se sindromom sistemskog upalnog odgovora (SIRS). Peritonitis se odvija zajedno s mnogim, složenim patofiziološkim promjenama na sistemskom i ćelijskom nivou.

Ključne riječi: Adhezija, citokini, peritonitis, PMN