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Postoperative peritonitis diagnosis features in abdominal sepsis

Características diagnósticas de la peritonitis postoperatoria en la sepsis abdominal

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SUMMARY

Introduction: *Despite significant advances in modern medicine, postoperative peritonitis is the cause of death in 50-86 % of patients. Postoperative peritonitis remains one of the most common causes of relaparotomy, accounting for 35 %-56 % of all intraabdominal complications. The diagnosis of postoperative peritonitis is based on clinical and biochemical examinations, the informative value of which is insufficient. One of the most informative methods of diagnosis of postoperative peritonitis with abdominal sepsis is a study of indices of endogenous intoxication and immune response of the body, such as medium-mass molecules, IgA, IgM, IgG, and complement activity.* **Objective***: The objective of the research is to study the changes in immune response in patients with postoperative peritonitis with abdominal sepsis.* **Methods:** *The clinic treated 456 patients with postoperative peritonitis who were treated at the Surgical Department of the communal non-profit organization Regional Clinical Hospital of Ivano-Frankivsk Region from 2000 to 2021. General clinical and biochemical examinations were performed in the laboratory of the Biological and Medicinal Chemistry Department of the Ivano-Frankivsk National Medical University. Immunological assessments were performed in 66 patients with postoperative peritonitis of varying severity of abdominal sepsis.* **Result:** *The results obtained for medium-mass molecules, IgA, IgM, IgG, and complement activity showed a marked difference between the groups ($p<0.001$), indicating their high sensitivity for the diagnosis of postoperative peritonitis with abdominal sepsis of varying severity.*

Keywords: *Postoperative peritonitis, abdominal sepsis, medical diagnosis, relaparotomy, postoperative morbidities.*

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RESUMEN

Introducción*: A pesar de los importantes avances de la medicina moderna, la peritonitis postoperatoria es la causa de muerte en el 50 %-86 % de los pacientes. La peritonitis postoperatoria sigue siendo una de las causas más frecuentes de relaparotomía, representando el 35 %-56 % de todas las complicaciones intraabdominales. El diagnóstico de la peritonitis postoperatoria se basa en exámenes clínicos y bioquímicos, cuyo valor informativo es insuficiente. Uno de los métodos más informativos de diagnóstico de la peritonitis postoperatoria con sepsis abdominal es el estudio de los índices de intoxicación endógena y respuesta inmunitaria del organismo, como las moléculas de masa media, IgA, IgM, IgG y la actividad del complemento.* **Objetivo:** *El objetivo de la investigación es estudiar los cambios en la respuesta inmune en pacientes con peritonitis postoperatoria con sepsis abdominal.* **Métodos:** *La clínica trató a 456 pacientes con peritonitis postoperatoria que fueron tratados en el departamento quirúrgico de la organización comunal sin fines de lucro Hospital Clínico Regional de la región de Ivano-Frankivsk desde 2000 hasta 2021. Los exámenes clínicos y bioquímicos generales se realizaron en el laboratorio del Departamento de Química Biológica y Medicinal de la Universidad Médica Nacional de Ivano-Frankivsk. Se realizaron evaluaciones inmunológicas en 66 pacientes con peritonitis postoperatoria de diversa gravedad de sepsis abdominal.* **Resultados:** *Los resultados obtenidos para moléculas de masa media,, IgA, IgM, IgG y actividad del complemento mostraron una marcada diferencia entre los grupos (p<0,001), indicando su alta sensibilidad para el diagnóstico de peritonitis postoperatoria con sepsis abdominal de gravedad variable.*

Palabras clave: *Peritonitis postoperatoria, sepsis abdominal, diagnóstico médico, relaparotomía, morbilidades postoperatorias.*

INTRODUCTION

Sepsis is a dysregulated immune response characterized by systemic inflammatory response syndrome (mild sepsis) mostly resulting from an infectious disease. In severe cases, it can lead to septic shock and systemic organ dysfunction. Sepsis is a significant cause of mortality in surgical intensive care units. Intra-abdominal sepsis includes localized and generalized peritonitis and is a systemic inflammatory response to infection. The effects, therefore, reflect an increased severity of the systemic response to the infection, but not the severity of the infection. Infection increases due to synergies between aerobes such as *Escherichia coli*, which reduce acidity and promote the growth of organisms such as *Bacteroides fragilis* and the presence of environmental companions such as faecal matter and gum (1,8). There is a balance between an excessive and inadequate response to infection. The immune response to sepsis can be seen as a pattern recognition receptor-mediated dysregulation of the immune system following pathogen invasion in which a careful balance between inflammatory and anti-inflammatory responses is vital. Production of several mediators is necessary to control infection, but excessive or prolonged activation of such cellular/humoral mediator pathways is thought to contribute to the development of organ failure in patients with major sepsis (4,9-13). Mortality increases with the degree of the systemic inflammatory response, which is a massive systemic reaction and consists of the establishment of cytokine cascade (TNF-α, IL-1, IL-6, IL-8) and stable activation of the mononuclear phagocyte system. The role of inflammatory mediators including cytokine and chemokine profiles, and their association with disease outcomes have been extensively studied in sepsis. Cytokines TNF-α and IL-1 are the most extensively studied pro-inflammatory mediators in sepsis. These cytokines are capable of activating target immune cells to produce additional inflammatory mediators and therefore, a heightened immune response. This leads to the production of secondary inflammatory mediators that cause cellular damage.

These mediators include arachidonic acid metabolites (prostaglandins, leukotrienes), nitric oxide, oxygen free radicals, and platelet-activating factor, which causes increased deposition of platelets, joint enlargement, an increase of capillary permeability and activation of laryngeal pathways which cause end-organ dysfunction through the formation of microthrombi (3,11). Systemic inflammatory response syndrome is mediated by cells of innate immunity, including neutrophils, monocytes, and macrophages. The production of pro-inflammatory cytokines and chemokines, including Tumor Necrosis Factor-alpha (TNF-α), IL-6, and IL-8, occasionally trigger adverse innate immune reactions to inhibit

infections and, as a result, tissue deterioration. However, in sepsis, excessive and prolonged production of these cytokines can lead to increased inflammatory reactions, which are more harmful than the initial infection. This is what happens in severe sepsis when excessive production of proinflammatory cytokines results in tissue damage and lethal organ failure (9,10,14). An elevated level of anti-inflammatory cytokines is indirectly correlated with the severity of survival and mortality in sepsis.

In fact, these cytokines contribute to the development of acute phase reactions with fever, leukocytosis, changes in metabolism, and activation of complement cascades and flaring. A sustained elevation of these cytokines results in a variety of pathological reactions leading to the induction of hypotension and shock. Understanding the peritoneal pathophysiology in surgical sepsis and identification of the sources of pathogenic organisms is of crucial importance for the prevention of intrabdominal infection. Individual variations in the pattern of mediator removal and end-organ reactions may play a significant role in determining the initial physiological response to sepsis, and, in turn, may be a key determinant of the outcome. The ability to detect the presence of peritonitis is likely to have the greatest impact on the residual surgical decision. Prevention of the progression of sepsis lies in early targeted therapy and control of the source of infection (6,15).

The research aims to study the changes in immune response in patients with postoperative peritonitis with abdominal sepsis.

MATERIALS AND METHODS

456 patients with postoperative peritonitis were treated at the Surgical Department of the communal non-profit organization Regional Clinical Hospital of Ivano-Frankivsk Region from 2000 to 2021. General clinical and biochemical examinations were performed in the laboratory of the Biological and Medicinal Chemistry Department of the Ivano-Frankivsk National Medical University. Immunological evaluations were performed on 66 patients, divided into 4 sub-groups, with postoperative peritonitis of varying severity of abdominal sepsis. Stored plasma samples obtained from participants were thawed on ice, and concentrations of the cytokines (IgA, IgM, and IgG) were determined using a Human Immunoglobulins commercial ELISA Antibody Kit and according to the kit manufacturer's protocol. Data analysis was performed using the statistical package software. The means and standard deviations were calculated for each group, and the Student t-test was used to detect a difference among means. A $p<0.05$ was considered significant.

RESULTS AND DISCUSSION

The occurrence of endogenous intoxication syndrome in postoperative peritonitis patients with varying degrees of severity of abdominal sepsis was confirmed by elevated blood levels of medium mass molecules and decreased complement system activity. In patients with postoperative peritonitis complicated by moderate levels of abdominal sepsis, the blood levels of medium-mass molecules increased. The index reached its maximum value on the third day of the disease and amounted to 0.269 ± 0.019 units. On the 11^{th} day of the disease, the index decreased but still was 1.25 times higher than the control (Table 1). Changes in humoral immunity were accompanied by a temporary decrease in blood levels of class G immunoglobulins due to a steadily decreased complement activity.

IgA levels in patients with postoperative peritonitis complicated by moderate-severity abdominal sepsis remained within the normal range during the entire period of observation. At the beginning of the disease, IgM was within the normal values, but on the 11th day, it increased to 2.33 ± 0.09 g/L, which was accompanied by a decrease in endogenous intoxication (Table 1). On the first day of illness, postoperative peritonitis patients with mild-to-moderate abdominal sepsis experienced a rapid decline in IgG levels 1.6-fold below control. Later, there was an increase in IgG. On the 11th day, the index was equal to the control and 10.41 ± 0.56 g/L (Table 1). The activity of the complement system was decreased during the entire period of observation. The lowest level was reached on the 1st day of the disease and was 0.80 ± 0.03 g/L. A gradual increase

was observed in the subsequent period (Table 1). In patients with postoperative peritonitis with severe abdominal sepsis, who were hospitalized in critical condition, there were blood levels of medium mass molecules. This index reached its maximum value during the first day of the disease and amounted to 0.307 ± 0.015 g/L. On the 11th day of the disease, the index decreased but still was 1.5 times higher than the control (Table 2). Changes in humoral immunity were accompanied by a steadily decreased level of all classes of immunoglobulins in the blood based on a decrease in complement activity for an hour.

Table 1. The content in the blood of molecules of medium mass, immunoglobulins, and complement activity in patients (group 1) with postoperative peritonitis complicated by moderate to severe abdominal sepsis (x ± Sx)

Indicators that have been studied	Control n = 35	Time frame of observation 1st day n = 26	3rd day n = 26	11th day n = 26
Molecules of medium mass, conventional units	0.198 ± 0.012	0.267 ± 0.013 p<0.001	0.269 ± 0.019 p<0.01	0.248 ± 0.014 p<0.01
IgA, g/L	1.49 ± 0.06	1.39 ± 0.06 p>0.2	1.51 ± 0.07 p>0.8	1.44 ± 0.08 p>0.6
IgM, g/L	1.21 ± 0.04	1.21 ± 0.05 p>0.9	1.33 ± 0.06 p>0.08	2.33 ± 0.09 p<0.001
IgG, g/L	11.15 ± 0.73	7.20 ± 0.31 p<0.001	9.17 ± 0.43 p<0.05	10.41 ± 0.56 p>0.4
Complement activity, conventional units	1.09 ± 0.05	0.80 ± 0.03 p<0.001	0.91 ± 0.04 p<0.02	0.93 ± 0.05 p<0.05

p is the degree of variance of the indicators with respect to control; n is the number of observations.

The IgA level in patients with postoperative peritonitis with severe abdominal sepsis remained within the normal range by 1st day of the disease. Thereafter, there was a decrease in the index to 1.06 ± 0.04 g/L by the 11th day (Table 2). There was a gradual decline in IgM throughout the entire period of observation. The lowest level was reached on the 11th day of the disease, reaching 0.71 ± 0.04 g/L (Table 2). The IgG level on the first day of the disease was 1.1 times lower than that of the control. Afterward, there was a gradual decrease in IgG. On the 11th day, the index was 8.48 ± 0.37 g/L (Table 2). In patients with postoperative peritonitis with severe abdominal sepsis, complement system activity at the onset of the disease was similar to that of the control group. On the 11th day, there was an increase in its dynamism to 1.23 ± 0.05 units (Table 2). The development of intoxication syndrome is confirmed by a high and settled level of medium molecules in the blood and inhibition of the humoral line of the immune response.

The blood count of medium-mass molecules in patients with postoperative peritonitis with an extremely severe course of abdominal sepsis exceeded the control by 34.8 % on the 1st day, by 79.3 % on the 3rd day, and by 54 % on the 11th day (Table 3). Plasma concentrations of immunoglobulins A and M on the first day of the monitoring did not differ from the control, on the third day there was an increase, and their normalization was on the 11th day of treatment. Changes in humoral immunity were accompanied by a steadily decreased level of immunoglobulin

G due to a gradual decrease in complement activity. IgA levels in patients with postoperative peritonitis with extremely severe abdominal sepsis remained within normal limits on the 1st day of the disease. On the third day, this index exceeded the control level by 25.5 % and normalized on the 11th day with postoperative peritonitis with an extremely severe course of abdominal sepsis. IgM on the first day of the disease exceeded the control level by 13.2 % and continued to increase until the third day. On the 11th day, it normalized (Table 3).

Table 2. Changes in the content in the blood of molecules of medium mass, immunoglobulins, and complement activity in patients (group 2) with postoperative peritonitis with severe abdominal sepsis (x ± Sx)

Indicators that have been studied	Control n=35	Time frame of observation 1st day n = 26	3rd day n = 26	11th day n = 26
Molecules of medium mass, conventional units	0.198 ± 0.012	0.307 ± 0.015 p<0.001	0.302 ± 0.014 p<0.001	0.294 ± 0.011 p<0.001
IgA, g/L	1.49 ± 0.06	1.51 ± 0.07 p>0.8	1.28 ± 0.05 p<0.05	1.06 ± 0.04 p<0.001
IgM, g/L	1.21 ± 0.04	0.85 ± 0.07 p<0.001	0.80 ± 0.05 p<0.001	0.71 ± 0.04 p<0.001
IgG, g/L	11.15 ± 0.73	10.19 ± 0.49 p>0.4	9.65 ± 0.63 p>0.2	8.48 ± 0.37 p<0.05
Complement activity, conventional units	1.09 ± 0.05	1.08 ± 0.06 p>0.9	1.10 ± 0.04 p>0.9	1.23 ± 0.05 p>0.09

p – degree of variance of indicators in relation to control; n is the number of observations.

On the first day of the disease, IgG was 1.5 times lower than control, but by the 3rd day, it had increased to 9.33 ± 0.42 g/L with a fall to the previous level by the 11th day. In patients with postoperative peritonitis with extremely severe abdominal sepsis, complement system activity at the start of the disease was similar to control. On the 11th day, there was a drop to 1.00 ± 0.05 conventional units (Table 3).

In postoperative peritonitis patients with terminal abdominal sepsis, the plasma level of medium mass molecules on the 1st day exceeded the control level by 73.7 %, with a 30.8 % increase on the 3rd day, and a 56.6 % increase on the 11th day. The amount of immunoglobulin A in the blood plasma on the 1st day of the monitoring was 56.4 % higher than in the control group, it decreased on the 3rd day but remained 19.5 % higher than the control. On the 11th day, there was a sharp decrease up to (0.98 ± 0.05) g/L. The blood plasma level of immunoglobulin M was 57.0 % higher than in the control group on the first day of the examination, and decreased further on the 3rd day, but remained 28.1 % higher than in the control group. On the 11th day, there was a sharp decrease up to 0.93 ± 0.05 g/L. The immunoglobulin of class G on the 1st day of the disease exceeded the control by 10 %, but on the 3rd day, it decreased by 10 % less than in the control group. The index continued to decrease rapidly, and on the 11th day of the disease reached 4.97 ± 0.32 g/L. In patients with postoperative

Table 3. The content in the blood of molecules of medium mass, immunoglobulins, and complement activity in patients (group 3) with postoperative peritonitis with extremely severe abdominal sepsis (x ± Sx)

Indicators that have been studied	Control n = 35	Time frame of observation 1-a addition n = 26	3rd addendum n = 26	11-a addition n = 26
Molecules of medium mass, conventional units	0.198 ± 0.012	0.267 ± 0.020 p<0.01	0.355 ± 0.021 p<0.001	0.305 ± 0.011 p<0.001
IgA, g/L	1.49 ± 0.06	1.37 ± 0.06 p>0.2	1.87 ± 0.09 p<0.01	1.29 ± 0.05 p>0.05
IgM, g/L	1.21 ± 0.04	1.30 ± 0.05 p>0.2	1.37 ± 0.06 <0.05	1.19 ± 0.05 p>0.7
IgG, g/L	11.15 ± 0.73	7.71 ± 0.30 p<0.01	9.33 ± 0.42 p>0.1	6.98 ± 0.28 p<0.001
Complement activity, conventional units	1.09 ± 0.05	1.11 ± 0.04 p>0.8	1.09 ± 0.03 p>0.9	1.00 ± 0.05 p>0.2

p – degree of variance of indicators in relation to control; n is the number of observations.

peritonitis with a temporary state of abdominal sepsis, the complement system activity at the beginning of the disease was reduced by 16 % from the control level. A gradual increase was subsequently observed. On the 11th day, this indicator reached normal values (Table 4).

Table 4. Dynamics of changes in the blood content of molecules of medium mass, immunoglobulins, and complement activity in patients with postoperative peritonitis (group 4-a) with terminal abdominal sepsis (x ± Sx)

Indicators that have been studied	Control n = 35	Time frame of observation 1st day n = 26	3rd day n = 26	11th day n = 26
Molecules of medium mass, conventional units	0.198 ± 0.012	0.344 ± 0.018 p<0.001	0.259 ± 0.012 p<0.02	0.310 ± 0.011 p<0.001
IgA, g/L	1.49 ± 0.06	2.33 ± 0.10 p<0.001	1.78 ± 0.07 <0.02	0.93 ± 0.05 p<0.001
IgM, g/L	1.21 ± 0.04	1.90 ± 0.04 p<0.001	1.55 ± 0.03 p<0.001	0.98 ± 0.03 p<0.01
IgG, g/L	11.15 ± 0.73	12.30 ± 0.69 p>0.4	10.03 ± 0.45 p>0.4	4.97 ± 0.32 p<0.001
Complement activity, conventional units	1.09 ± 0.05	0.92 ± 0.04 p>0.07	0.93 ± 0.05 p>0.09	1.00 ± 0.05 p>0.3

p – degree of variance of indicators in relation to control; n is the number of observations.

Hence, the content in the blood of molecules of medium mass increases dramatically in the terminal state of abdominal sepsis, and the initial activation of the humoral immune response is followed by a marked decrease in immunoglobulin A and M due to a catastrophic decrease in immunoglobulin G concentrations. The decreased concentrations of the main classes of immunoglobulins in the blood vessels are considered by clinicians as an indication for immunoreaction for improvement of treatment results in patients with postoperative peritonitis with abdominal sepsis.

Postoperative peritonitis is a serious and potentially fatal complication that occurs after surgical interventions on the organs of the abdominal cavity. The high lethality of the disease makes postoperative peritonitis one of the most dangerous complications in abdominal surgery (16). One of the unclear and understudied features of abdominal sepsis is that it can occur (recur) in the remote period after the first surgical intervention (17). In the conditions of the development of multiorgan failure syndrome, which occurs against the background of enteric failure and endogenous intoxication, infectious-toxic shock occurs, and severe abdominal sepsis develops. Generalization of the infection occurs when the activity of the causative agent prevails over the bacteriostatic capabilities of the human body. The current definition recognizes the severity implicit by the term sepsis, namely that sepsis is initiated by an invading pathogen and results in a process in which the body's response is inappropriate. This pathophysiological response can culminate in multi-organ failure, usually due to a combination of cardiovascular, cellular, coagulation, and endothelial dysfunction, aptly described as the four horsemen of the septic apocalypse.

Abdominal sepsis develops in the event of a breakdown in one of the links of immunity: a decrease in the phagocytic activity of neutrophils, a dysregulation of antibody synthesis, or the proliferation of lymphocytes (18). Evidence indicates that disruptions in the normal homeostatic mechanisms of the immune and neuroendocrine systems during sepsis, alter cellular energy processes, disrupting endothelial and epithelial functions, which can ultimately cause dysfunction at the organ level (19). The more protracted immunosuppressive phase is a complex, multifactorial process stemming from immune cell depletion, due to uncontrolled apoptotic events as the primary mechanism of sepsis-induced immune suppression. Understandably if the key role players in the innate and natural inflammatory response are involved, the likelihood of the patient succumbing to secondary infections is greatly increased.

Early diagnosis and surgical intervention play a key role in the treatment of patients. Previous studies have identified several clinical signs that may aid in the diagnosis of postoperative peritonitis in patients with abdominal sepsis.

The diagnostic program includes an immediate performance of a complex diagnostic laboratory (clinical blood, urine, liver tests, coagulogram, creatinine, urea) and instrumental and hardware studies (abdominal ultrasound examination, computer tomography, laparoscopy), bacteriological method study of fluid from the abdominal cavity (20). The inflammatory response in patients with sepsis depends on the causative pathogen and the host (genetic characteristics and coexisting illnesses), with differential responses at local, regional, and systemic levels. The host inflammatory response probably changes over time in parallel with the clinical course. Sepsis, in the early stages of the inflammatory process, should be considered a local/peritoneal disease. In advanced stages, severe sepsis and septic shock should be considered as systemic disease, and patients who are extremely unstable and exhibit high rates of mortality should be managed more aggressively. Since abdominal infection leads to the activation of an inflammatory response, this suggests that some of these mediators may be used as markers of the severity of new-onset sepsis, but primarily to identify or rule out new sepsis (17). Predictors of postoperative peritonitis with abdominal sepsis include abdominal distension, fever, and leucocytosis. Also, the key diagnostic signs of the disease include fever, abdominal pain, and tachycardia. In addition, the presence of free air or fluid in the abdominal cavity during imaging studies such as computed tomography or ultrasound may also indicate postoperative peritonitis (21).

In addition to these clinical signs, laboratory tests can also help in the diagnosis of postoperative peritonitis. The enzymes alanine aminotransferase and aspartate aminotransferase can act as early (preclinical) markers of the development of abdominal sepsis. We should also mention the traditional markers - procalcitonin and total cholesterol, which is explained by their participation in the metabolism of stress hormones and other biologically active metabolites. C-reactive protein and serum amyloid A are also valuable markers (17,22). Also, elevated lactate, a biomarker of tissue hypoxia, was a reliable predictor of sepsis in patients with postoperative peritonitis. A study also found that serum lactate levels were significantly associated with the development of organ dysfunction and mortality in these patients (21-23). An important aspect of the development of abdominal sepsis and mortality remains the formation of multiple organ deficiency syndrome (MODS). To diagnose MODS, it is enough to obtain one of the clinical and laboratory signs of organ dysfunction: acute respiratory distress syndrome, cardiovascular system dysfunction, liver dysfunction, kidney dysfunction, haemostasis system dysfunction, and central nervous system dysfunction (17,5,24).

Despite advances in diagnostic tools and treatment methods, postoperative peritonitis remains a difficult disease to treat. Delayed or missed diagnosis can lead to the progression of sepsis, multiple organ failure, and even death. Therefore, clinicians need to maintain a high index of suspicion for postoperative peritonitis in patients undergoing abdominal surgery, especially in those with risk factors for the disease (22,25,26). In general, postoperative peritonitis and abdominal sepsis are serious diseases that require prompt diagnosis and treatment. Advances in diagnostic tools such as biomarkers and imaging techniques have improved the ability to accurately identify these conditions, which in turn can lead to improved patient outcomes. In general, the diagnosis of postoperative peritonitis in patients with abdominal sepsis requires a multifactorial approach that includes clinical, imaging, and laboratory findings. Early recognition of key diagnostic features can facilitate prompt intervention and improve patient outcomes. However, further research is needed to develop more accurate and reliable means of diagnosing postoperative peritonitis in patients with abdominal sepsis (21,25).

CONCLUSIONS

To conclude, sepsis is a condition characterized by uncontrolled immune and inflammatory responses and has several challenges in its diagnosis and management. Postoperative peritonitis can occur without abdominal sepsis, with abdominal sepsis, and with septic shock. Even after surgical removal of the infection in the abdominal cavity and intensive antibiotic therapy, 50 % of patients with abdominal sepsis develop infectious-toxic shock or marked organ dysfunction, with fatal consequences among 50 %-90 %. The diagnosis of postoperative peritonitis is based on clinical and biochemical examinations, the informative value of which is insufficient. One of the most informative methods of diagnosis of postoperative peritonitis with abdominal sepsis is the study of indices of endogenous intoxication and immune response of the body, such as medium-mass molecules, IgA, IgM, IgG, and complement activity. The results obtained for such indices as medium molecules, IgA, IgM, IgG, and complement activity showed a marked difference between the groups under investigation ($p<0.001$), indicating their high sensitivity for the diagnosis of postoperative peritonitis with abdominal sepsis of varying severity. However, patients with postoperative peritonitis with extremely severe abdominal sepsis demonstrate a high level of intoxication, resulting in a hormonal immune response due to decreased plasma concentrations of class G immunoglobulins.

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