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Bilirubin, Interleukin 6 (IL 6) and Lipopolysaccharide – Binding Protein (LBP) – Biomarkers of Sepsis in Appendicular Peritonitis

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Abstract: *Peritonitis remains, despite the diagnostic and therapeutic developments, a serious condition, the main cause of septic shock with lethal potential in abdominal surgery Identifying and characterizing the dynamics of early biomarkers of the inflammatory response in abdominal sepsis is important to better follow-up evolution and postoperative infectious complications. The paper aims to study the dynamics of serum concentration of biomarkers LBP, IL6 and bilirubin in patients with acute peritonitis of appendicular cause, in the pre and postoperative stage and the correlation with the clinical evolution of inflammatory syndrome. A prospective 6-month study was performed, including patients for appendicular peritonitis. LBP, IL6, bilirubin, leukocytes were sampled preoperatively, then postoperatively at 72 h, and repeated at 72 h until values returned to normal. Clinical evolution and leukocytes were correlated with biochemical parameters. The mean preoperative values for the studied biochemical parameters were for Il6 of 14.81 +/- 4,047 pg / mL, for LBP of 33,826 +/- 5.5.02 microgram / mL and for bilirubin of 1.77 +/- 0.55mg / mL. The postoperative values decreased in all cases, but remained above normal limits in cases with septic complications. LBP, Il 6 and bilirubin are biomarkers useful in the pre- and postoperative evaluation of sepsis in appendicular peritonitis, correlating more accurately with the evolution of the inflammatory response than leukocytosis. Bilirubin is useful in monitoring intraperitoneal infection, but is not influenced by the existence of extraperitoneal infection. The dynamics of LBP is the most accurate description of bacterial infectious factor exposure.*

Keywords: *Lipopolysaccharide - Binding Protein (LBP), Interleukin 6 (Il 6), Bilirubin, biomarker, peritonitis*

1.Introduction

Peritonitis remains, despite the diagnostic and therapeutic developments, a serious condition, the main cause of septic shock with lethal potential in abdominal surgery. Direct contamination of the peritoneum from the initial septic focus may turn in spread to localized intraperitoneal or abdominal wall sepsis, continuing postoperatively. This fact is supported by positive bacteriology of peritoneal reaction fluid, pus from a periappendicular abscess, or suppurated surgical site [1].

Even in the conditions of correct surgical treatment, the severity of the inflammatory response, and the evolution of sepsis is difficult to predict, depending on the individual reactivity, the degree of contamination of the peritoneal cavity, the time elapsed since the moment of perforation, the biological status of the patient. On the other hand, the incidence of postoperative infectious complications is relatively high in cases of complicated appendicitis, ranging between 23.1% - 40.8%, of which approx. 5% evolving to severe sepsis with multiple organ dysfunction [1-4]. Identifying and characterizing the dynamics of early biomarkers of the inflammatory response in abdominal sepsis is important to better follow-up evolution and postoperative infectious complications [5-9].

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The paper aims to study the dynamics of serum concentration of biomarkers LBP, IL6 and bilirubin in patients with acute peritonitis of appendicular cause, in the pre and postoperative stage and the correlation with the clinical evolution of inflammatory syndrome.

2. Materials and methods

Methodology

A prospective 6-month study was performed, including patients hospitalized and operated on urgently for appendicular peritonitis. Sepsis was documented by the intraoperative sampling of intraperitoneal fluid for bacteriological exam. LBP, IL6, bilirubin, leukocytes were harvested preoperatively, then postoperatively at 72 h, and repeated at 72 h until values returned to normal. Clinical evolution (fever, pulse, local pain, resumption of transit) and leukocytosis were correlated with dosed biochemical parameters.

LBP and II6 assay were performed by chemiluminescence detection (CLIA) immunochemical method. After collection from the venous blood, on the anticoagulant-free test tube provided with segregation gel, the serum was separated by centrifugation for 15 min at 4,000 RPM, as soon as possible after the complete formation of the clot, and the sample was immediately frozen at -20°C. The analysis of the samples was performed in the first 24 h after collection. The reference values considered normal for the laboratory and the technique used were LBP <15 micrograms/ mL and Il-6 <9.7 pg/mL.

The dosage of total serum bilirubin was performed by the colorimetric method, considering normal serum values of <1.2 mg/dL.

3.Results and discussions

A total of 19 patients were enrolled in the study. The average age was relatively evenly distributed between 20-60 years, with an average of 48 years +/- 12,931 and a B: F sex ratio of 12: 7. In the bacteriological analysis of the peritoneal fluid, a mixed flora was isolated, with a constant presence of gram-negative germs. The most common germs identified were: Bacteroides (89.47%) and Escherichia coli (84.21%), which was present in 17 out of 19 patients who had pathology-proven acute appendicitis. Less frequent organisms were Klebsiella pneumoniae (3 cases; 15.78%), Streptococcus spp. (2 cases; 10.52%), Enterococcus spp. (2 cases; 10.52%) Histopathological examination supported the diagnosis of perforated appendicitis, with intense inflammatory serous attachment peritoneal in all cases.

The postoperative clinical evolution was favorable in 84.2% of cases. In 3 cases, septic complications were registered: 2 abdominal wall abscesses and an intra-abdominal septic collection that required reintervention and drainage.

For all cases, the values for total Il-6, LBP, and leukocytosis significantly increased above normal preoperatively and decreased 72 h after surgery. The same dynamics were observed for bilirubin in 94.7% of cases. Only in one patient, the bilirubin was normal both preoperatively and postoperatively. Increases in Il-6 and bilirubin were moderate, while LBP values frequently exceeded twice the normal value. Intense inflammation and necrosis of gangrenous appendicitis present at the anatomo-pathological exam correlate well with high levels of biological markers of inflammation. The mean preoperative values for the studied biochemical parameters were for Il6 of 14.81 +/- 4,047 pg / mL, for LBP of 33,826 +/- 5.5.02 microgram / mL and for bilirubin of 1.77 +/- 0.55mg / mL. The preoperative values of IL6 are above normal values, the excesses being moderate (between 10 and 15) but also high (between 15 and 25); after surgery, most patients have normal values but remain a few with moderate excesses (between 10 and 15). All preoperative LBP values are above normal, with excesses generally high (values between 30 and 40). The postoperative clinical evolution was favorable in 84.2% of cases. In 3 cases, septic complications were registered: 2 abdominal wall abscesses and 1 intra-abdominal septic collection that required reintervention and drainage.

Table 1. The values of Il6, LBP, Bilirubin and Leukocytes at the admission in the study group

	IL6	LBP	Bilirubin	Leukocytes
Media	14.81	33.826	1.7705	18114.74
Std. Deviation	4.047	5.0224	0.55595	3450.276
Median	13.50	35.700	1.7000	17500.00
Minimum	11	20.9	0.90	10680
Maximum	26	39.1	3.03	23100

At 72 h postoperatively, the values of LBP, IL6, and bilirubin decreased significantly in the patients in the study group, which correlated with the favorable clinical evolution in most cases.

Table 2. The values of Il6, LBP, Bilirubin and Leukocytes in the study group, 72 h after surgery

	IL6	LBP	Bilirubin	Leukocytes
Mean	8.00	12.547	0.7005	11417.89
Std. Deviation	2.132	2.8541	0.22160	2068.546
Median	7.70	12.400	0.7400	11500.00
Minimum	5	7.1	0.26	7700
Maximum	14	17.5	1.10	14600

The tests of statistical significance (t-test, nonparametric Wilcoxon test) show a significant change in the values of biochemical markers between preoperative and postoperative time. The averages of the differences between the values at admission and the values after 72 h from the intervention are negative, so the tendency of normalization of values is rapid, in the case of favorable postoperative evolution, once the exposure to septic factor is removed.

Table 3. Statistical significance of the differences in values at 72 h and preoperative for the studied biomarkers (Pearson test)

Variable: Difference 72 hours Postop-Preop value[1)]	Test Value = 0				
				95% Confidence Interval of the Difference	
	Mean Difference	t	Sig. (2-tailed)	Lower	Upper
Diff_ bilirubin	-1,07000	-9,818	,00	-1,2990	-,8410
Diff_IL6	-6,81053	-12,317	,00	-7,9722	-5,6489
Diff_LBP	-21,27895	-23,367	,00	-23,1921	-19,3658
Diff_Leukocytes	-6696,84211	-14,635	,00	-7658,2239	-5735,4603

Table 4. Statistical significance of the differences in values at 72 h and preoperative for the studied biomarkers (Wilcoxon signed-rank test)

	Diff_ Il6	Diff_ LBP	Diff_ Leukocytes	Diff_ Bilirubin
Z	-3.824[a]	-3.823[a]	-3.823[a]	-3.823[a]
Asymp. Sig. (2-tailed)	0.000	0.000	0.000	0.000

The correlations between the values of the 4 parameters IL6, LBP, bilirubin and leukocytes for the individuals in the study group were statistically analyzed, using the Pearson test. Values with statistical significance ($p < 0.05$) were recorded for LBP and bilirubin, both for the preoperative and postoperative stages.

The distribution of the variables IL6, LPB, Total Bilirubin and No Leukocytes can be considered normal according to Kolmorov-Smirnov test, both preoperatively and postoperatively.

Table 5. Statistical correlation of the preoperative values of LBP, IL6, Bilirubin and leukocytes

		Bilirubin	IL6	LBP	Leukocytes
Bilirubin	Pearson Corr.	1	0.222	0.540*	-0.430
	Sig. 2-tail		0.361	**0.017**	0.066
IL6	Pearson Corr.	0.222	1	0.366	0.108
	Sig. 2-tail	0.361		0.123	0661
LBP	Pearson Corr.	0.540*	0.366	1	-0.262
	Sig. 2-tail	**0.017**	0.123		0.279
Leukocytes	Pearson Corr.	-0.430	0.108	-0.262	1
	Sig. 2-tail	0.066	0.661	0.279	

* Correlation is significant at the 0.05 level (2-tailed)

Table 6. Statistical correlation of the 72 h postoperative values of LBP, IL6, Bilirubin and leukocytes

		Bilirubin	IL6	LBP	Leukocytes
Bilirubin	Pearson Corr.	1	0.165	0.479*	-0.332
	Sig. 2-tail		0.499	**0.038**	0.164
IL6	Pearson Corr.	0.165	1	-0.057	0.144
	Sig. 2-tail	0.499		0.816	0.556
LBP	Pearson Corr.	0.479*	-0.057	1	-0.190
	Sig. 2-tail	**0.038**	0.816		0.436
Leukocytes	Pearson Corr.	-0.332	0.144	-0.190	1
	Sig. 2-tail	0.164	0.556	0.436	

Table 7. Kolmogorov-Smirnov test for normality of the distribution of the investigated biomarkers

		PreopIL 6	Postop IL6	Preop LBP	Postop LBP	Preop Bilirubin	Postop Bilirubin	Preop Leukocytes	Postop Leukocytes
Normal Parameters[a,,b]	Mean	14.811	8.000	33.82632	12.54737	1.7705	0.7005	18114.74	11417.89
	Std. Dev.	4.0467	2.1320	5.022377	2.854114	0.55595	0.22160	3450.276	2068.546
Most Extreme Differences	Absolute	0.170	0.116	0.209	0.104	0.144	0.110	0.115	0.117
	Positive	0.170	0.116	0.147	0.104	0.144	0.108	0.097	0.099
	Negative	-0.143	-0.067	-0.209	-0.061	-0.074	-0.110	-0.115	-0.117
Kolmogorov-Smirnov Z		0.739	0.507	0.913	0.452	0.626	0.481	0.499	0.512
Asymp. Sig. (2-tailed)		0.646	0.959	0.375	0.987	0.827	0.975	0.964	0.956

However, the examination of the maximum values shows that in the postoperative interval of 72 h not all patients reach the normal values of the four investigations. Next, we analyzed for each patient in the study group, the variation of preoperative parameters and determined at 72 h, and how these values are arranged compared to the upper limit of values considered normal in the general population. It is observed that the inflammation marker that normalizes the fastest is total bilirubin, only one patient has high values postoperatively, the case being the one with intraperitoneal abscess for which surgery was re-operated. Bilirubin was normal in patients who developed parietal abscess without affecting the peritoneal cavity. We can conclude that bilirubin is a useful inflammatory marker for intraperitoneal sepsis, registering moderate increases, but does not change in the case of extraperitoneal infections.

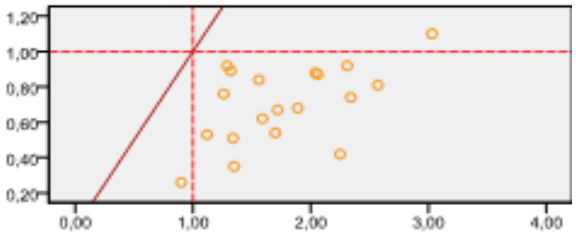

Figure 1. Variation of Bilirubin values: preoperative (horizontal axis) vs. 72 h postoperatively (vertical axis)

Another biomarker that normalizes early with the regression of the inflammatory response is IL6. At 72 h, only 2 patients (10%) still have values above the normal limit. The result can be clinically correlated with continued exposure to the infectious factor: one patient with intra-abdominal abscess, another patient with parietal abscess at the incision. Therefore, IL6 is a useful biomarker in diagnosing sepsis, but with relative value in the case of a moderate inflammatory process. The dynamics of the biomarker is characterized by rapid return to normal values in the case of favorable postoperative evolution. Recording elevated IL6 values at 72 h is strong argument for a septic complication.

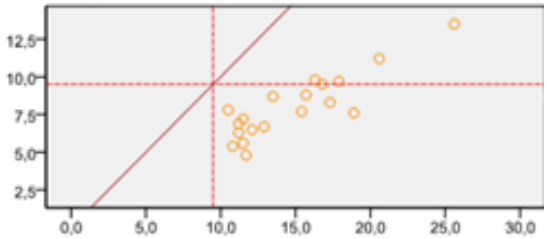

Figure 2. Variation of Il6 values: preoperative (horizontal axis) vs. 72 h postoperatively (vertical axis)

Serum LBP values correlate well with clinical evolution, remaining elevated above normal values in the case of the 3 patients who developed septic complications and returning in the range of normal values in the rest. The dynamics of LBP correlates best with exposure to the bacterial infectious factor, regardless of its localization or extraperitoneal. LBP decreases rapidly within normal values in case of eradication of the infectious outbreak and remains high in case of development of septic complications, being a good parameter for biochemical monitoring of postoperative evolution.

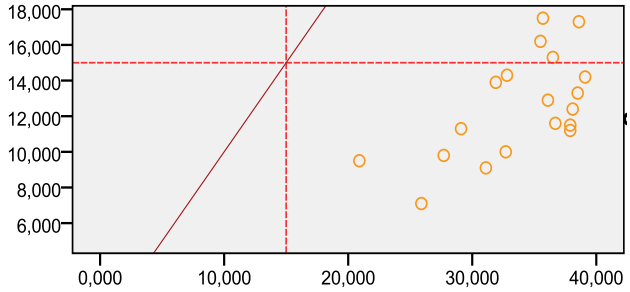

Figure 3. Variation of LBP values: preoperative (horizontal axis) vs. 72 h postoperatively (vertical axis)

The number of leukocytes in the blood is the slowest return to normal after surgical treatment of appendicular peritonitis. From a clinical point of view, it is important to understand that the presence of high values postoperatively early does not mean the development of an infectious complication. Acute phase biochemical markers Il 6, bilirubin and LBP are more sensitive and useful in postoperative monitoring of patients with abdominal sepsis and should be part of the clinical follow-up protocol.

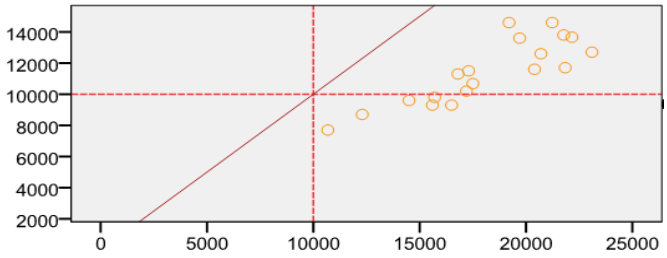

Figure 4. Variation of Leukocytes values: preoperative (horizontal axis) vs. 72 h postoperatively (vertical axis)

Bilirubin (C33H36N4O6)

Bilirubin is the degrading product of hemoglobin, a red-brown bile pigment and the most abundant antioxidant in tissues, being responsible for most of the antioxidant activity that takes place in the blood. Hyperbilirubinemia is caused either by excessive bilirubin production or by altered clearance. Both mechanisms lead to the accumulation of bilirubin and play a role in the hyperbilirubinemia observed in patients with appendicular peritonitis. A variety of bacterial infections have been shown to accompany liver dysfunction to the point of abnormalities in bile acid formation and bile flow[10]. Patients in septic shock and those with extrahepatic bacterial infections, such as acute gangrenous appendicitis, express a proinflammatory cytokine and cholestasis triggered by nitric oxide, by blocking the formation of bile, intraductal and hepatocellular [10].

Moreover, the most common bacterial species isolated from the appendicular wall, from patients with acute appendicitis, were Escherichia coli and Bacteroides fragilis, both known to interfere with hepatocyte microcirculation, inducing sinusoidal lesions [11]. A possible explanation for this is the circulating endotoxemia, related to appendix infection. Several studies demonstrated in vitro, using an infusion of endotoxins on an isolated mouse liver, that there is a dose-dependent decrease in the excretion of bile salts from the liver and that the endotoxin of Escherichia coli may be directly affected at the cholangiolar level [11,12]. In addition, Escherichia coli infection has been shown to induce hemolysis of normal erythrocytes. This results in increased bilirubin loading in infected individuals, a process that promotes hyperbilirubinemia.

Several recent studies [13-15] have demonstrated in a group of patients diagnosed with acute appendicitis the existence of hyperbilirubinemia in perforated and gangrenous forms. They described the rate of appendicular perforation as being 3 times higher for patients with hyperbilirubinemia compared to normal bilirubin levels. Diagnostic accuracy of hyperbilirubinemia in predicting perforated appendicitis was demostrated by several clinical studie [15-19]. More important, in the present study, hyperbilirubinemia proved to be an important biomarker for intraperitoneal sepsis diagnosis and monitoring. It was a constant founding in all patients with appendicular peritonitis and it was also the first parameter which reached normal values after septic exposure was eliminated.

Interleukin 6 (Il-6)

Interleukin-6 is a cytokine belonging to the family of 4α-helix long-chain hematopoietic cytokines composed of 212 amino acids, its gene can be mapped on chromosome 7p21 and contains 4 introns and 5 exons. It can be observed as a glycosylated and phosphorylated cariable protein of 22 to 27 kDa [20,21]. The IL-6 gene is not constitutively expressed, but its expression can be induced by a multitude of stimuli, including viral infections, LPS, IL-1b, TNF-α, PDGF and IFN-g [22]. Catecolamines also stimulate the production of IL-6, while sex hormones and corticosteroids inhibit its production.

IL-6 is normally a circulating plasma protein. But dosing serum levels of IL-6 is problematic. Even though large quantities, nanomolars are present in the serum of healthy individuals, it can be undetectable by biochemical and ELISA methods. A difficulty in dosing IL-6 is due to the existence of monomeric, dimeric and multimetric forms. Moreover, even if IL-6 is present in the blood at concentrations sufficient to exercise all roles in the healthy individual, IL-6 remains relatively inert. This suggests the presence of chaperone proteins, which alter or limit biological activity and camouflage it by some systems [23]. Interleukin-6 can exist in complexes with high molecular mass, along with various proteins such as C Reactive Protein, complement components and soluble IL-6 receptor. Due to these chaperones, depending on the technique used, concentrations may differ by up to 10 times [24]. These findings suggest that free IL-6 can only have a transient blood presence.

Interleukin-6 has a wide variety of effects on the immune system. It plays an important role in the maturation of immune cells. Induces the production of immunoglobulin by B cells and the differentiation of T cells, activates mitogenically stimulated T cells by inducing the production of Interleukin-2 and the expression of Interleukin-2 receptors [25]. Acts synergistically with Interleukin-2 in propelling T cell differentiation into cytotoxic lymphocytes. Interleukin-6 activates endothelial cells

and induces chemokine production, as well as adhesion of expressed molecules, leading to the recruitment of leukocytes at inflammation sites.

Classic IL-6 signaling is initiated by IL-6 binding to the membrane-bound form of the IL-6-specific receptor alpha subunit (IL-6 R alpha), which triggers its association with the signal-transducing gp130 receptor subunit. Stoechiometric experiments suggest that the functional complex is hexameric, composed of 2 units of IL-6, IL-6Ra and gp130 [25]. The binding of the ligands to the receptors leads to the activation of the cytoplasmic chain of tyrosine kinases (Jak). Specifically, IL-6 activates Jak1, Jak2 and Tzk2 which leads to the phosphorylation of the signal transducer and activation of STAT transcriptproteins, with the initiation of the synthesis of acute phase molecules [26, 27].

The production and action of all components of the IL-6-IL-6 receptor axis is strongly regulated by trauma and inflammation [28]. Increased levels of IL-6 are found in almost every case involving inflammatory, infectious and traumatic stages, occurring within minutes and remaining high for a few days [29-34]. Clinical studies showed that Il-6 proved to be an useful tool for monitoring antibiotical treatment efficacy in critically ill adults. There is an evidence of positive correlation of high Il-6 and bacterial peritonis in chronic dialised patients and in other septic diseases. Il6 is a good biomarker to predict complicated appendicitis [15,30]. Jekarl et al. reported that survivors of sepsis showed a rapid IL-6 reduction, while non-survivors showed persistently high IL-6 concentrations.These findings could be confirmed by Oda et al.and Pallás Beneyto et al [33,34]. On the other hand, Il6 seems to be specific to inflammation, not necesarily to sepsis. Il-6 is also increased in rheumatological diseases, and sensitivity to differentiate between Systemis inflamatory Syndrome (SIRS) and sepsis is limited [24, 32].

As a consequence, systemic dissemination of circulating IL-6 promotes the scattering of focal inflammation areas. The temporal change in IL-6 concentration creates some possible predictions regarding the regulation of cellular response. In the present study, Il6 proved to e an useful biomarker for monitoring postoperative septic complications after apendicular peritonitis and correlated well with the clinical outcome in the study group.

Lipopolysaccharide - Binding Protein (LPB)

LBP is considered the first acute phase protein identified that is capable of bacterial recognition, whose gene is transcriptionally activated by APRF / STAT 3 (Acute Phase Response Element / Signal Transducer and Activator of Transcription 3) under the action of cytokines IL1 (beta) , by the synergistic action of IL-1 and IL-6, and glucocorticoids, leading to a maximum concentration of LBP at 24-48h after stimulation [35]. Other stimuli that induce LBP synthesis in vivo are: lipopoly-saccharides, gram-negative bacteria, non-infectious agents such as turpentine [15]. Hepatic transcriptional induction of LBP is inhibited by TGF β1 (Transforming Growth Factor β1), an anti-inflammatory cytokine.

LBP belongs to the lipid transfer / lipopolysaccharide-binding protein family, along with BPI, CETP (cholesteryl ester transfer protein) and PLTP (phospholipid transfer protein). LBP is a 50 kDa polypeptide, being released into the bloodstream after glycolysis as a 58 to 60 kDa glycoprotein [36]. The lipopolysaccharide binding domain was identified at the N-terminus of LBP. This is structurally and functionally comparable to BPI (bactericidal permeability increasing protein). Both the LBP gene and the BPI gene are located closely on chromosome 20.

LBP binds with high affinity to the amphipathic part of the vast majority of lipopolysaccharides. LBP has been shown to facilitate the process of monomerization of LPS and subsequent presentation to other cellular and humoral binding sites. At the same time, it catalyzes the transfer of LPS to a membrane binding site (m) CD 14, which represents a part of the cellular LPS receptor. The ability of LBP to transfer disaggregated LPS to both mCD-14 and the soluble form of CD-14 supports the view that LBP has a central role in mediating LPS responses. It is assumed that a single LBP molecule is capable of transporting hundreds of LPS molecules to CD 14, and that LBP is not consumed in this

reaction Two models have been proposed to explain the catalyst reaction mechanism for LPS transfer to CD 14, namely : a binary complex - a model that suggests that LBP first interacts with an LPS micelle in a bimolecular reaction and dissociates from the micelle with a bound LPS molecule, which will bind to s CD 14 or a tertiary complex - a model that involves a simultaneous interaction of LBP, LPS micelles and CD 14 s [36,37]. LBP binding to LPS is not restricted to molecules, but also includes viable bacteria. The binding of LBP to Salmonella spp and Klebsiella pneumoniae has already been demonstrated, resulting in phagocytosis and clearance of these microorganisms [38].

High concentrations of LBP inhibit LPS-induced host cell activation. These can be partially explained by the ability of LBP to transfer LPS to serum lipoproteins, thus neutralizing LPS bioactivity. It has been shown that LBP is associated with lipoproteins containing apo A- or apo B- and that it transfers LPS to HDL and LDL, with the aim of clearing LPS from the bloodstream [39]. In addition to the classic role of LBP in accelerating LPS binding and LPS transfer and increasing the sensitivity of monocytes and neutrophils to endotoxin, new functions of this protein have also been discovered. Binding and transfer of bacterial components by LBP is not limited to bacteria that contain LPS, but also include gram-positive microorganisms such as Pneumoniae spp, Spirochete: B. burgdorferi, the role of LBP being increased to an important soluble molecule for pattern recognition. No significant differences in serum LBP were found in patients with gram-negative, gram-positive, or fungal infections [40].

To date, several studies have evaluated the value of LBP as a diagnostic biomarker. The results of these observational studies have been carefully analyzed due to the fact that the samples are small. Studies in children suggest that LBP is a sensitive and specific marker that helps differentiate between SIRS and a bacterial infection. Especially in premature infants and oncology patients at the onset of febrile neutropenia, elevated blood LBP may serve as an early marker for the diagnosis of bacterial infections. In adult patients in intensive care units, elevated LBP concentrations are correlated with the onset of bacteremia or severe sepsis and septic shock. In the present paper LBP is used not only for diagnosis, but also for monitoring post operatory evolution and as a prognostic factor for development of a septic complication [40-42].

Biological markers have the potential to improve the diagnostic and prognostic capacity of clinical assessment and the conventional inflammation tests [42,43]. Monitoring serum concentrations in dynamics is much more useful than isolated inpatient dosing. There are individual variations in the inflammatory response, but following the upward or downward trend for a particular patient may provide early information about the favorable response to therapy or the occurrence of a complication.

4.Conclusions

In appendicular peritonitis, LBP levels increase sharply, while Il6 and bilirubin increase moderately. Normalization of values at 72 h correlates with favorable evolution, while maintaining values above normal values indicates the development of an infectious complication.

LBP, Il 6 and bilirubin are biomarkers useful in the pre- and postoperative evaluation of sepsis in appendicular peritonitis, correlating more accurately with the evolution of the inflammatory response than leukocytosis. Bilirubin is useful in monitoring intraperitoneal infection, but is not influenced by the existence of extraperitoneal infection. The dynamics of LBP is the most accurate description of bacterial infectious factor exposure.

The research results allow the reporting of data and to correlate the values of inflammation biomarkers with the prognosis and clinical evolution. These values can also be extrapolated to other surgical pathology with severe septic risk. Further studies are needed to document the estimated values of these biomarkers in other causes of abdominal sepsis.

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