

## Could Ascitic Fluid Lactoferrin Help in Diagnosis of Spontaneous Bacterial Peritonitis? Review Article

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### ABSTRACT

**Background:** When an ascitic fluid is infected with bacteria, it's known as spontaneous bacterial peritonitis (SBP). Polymorphonuclear leukocyte (PMN) count of at least 250 cells/mm<sup>3</sup> is required for diagnosis of SBP despite the positive results of bacterial culture in the ascitic fluid. The number of PMNs in the ascitic fluid is counted after bringing it to the laboratory. True-negative results can be produced by the lysis of PMNs in the laboratory. The operator is responsible for manually counting the PMN in the ascitic fluid, which can cause a delay in the diagnosis. Proteins that bind iron, such as lactoferrin, are detected in both human mucosal secretions and PMN-specific granules. Lactoferrin concentration in faeces has been shown to be very sensitive and specific for the identification of intestinal inflammation in previous research.

**Objective:** Diagnosis of spontaneous bacterial peritonitis could be improved by using ascitic fluid lactoferrin.

**Methods:** PubMed, Google scholar and Science direct were searched using the following keywords: Ascitic fluid lactoferrin, spontaneous bacterial peritonitis and polymorphonuclear leukocytes. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included.

**Conclusion:** A biomarker for the existence of PMNs and the detection of SBP in cirrhotic individuals would be lactoferrin in the ascitic fluid.

**Keywords:** Ascitic fluid lactoferrin, Spontaneous bacterial peritonitis.

### INTRODUCTION

Peritonitis caused by a bacterial infection of the fluid within the abdomen is known as spontaneous bacterial peritonitis (SBP) <sup>(1)</sup>. In individuals with cirrhosis, spontaneous bacterial peritonitis is a well-known and worrisome consequence. Child-Pugh class C cirrhosis patients account for 70% of cases of spontaneous bacterial peritonitis in patients with the disease. When this occurs in these people, it is connected with a bad long-term outcome. At significant risk of death is the cirrhotic patient who develops spontaneous bacteriophageal peritonitis after septic shock <sup>(2)</sup>.

As much as 18% of people with ascites may be affected. In the last two decades, this number has increased from 8%, most likely as a result of heightened awareness of spontaneous bacterial peritonitis and lowering diagnostic paracentesis thresholds <sup>(3)</sup>.

The aimed of review was to diagnose spontaneous bacterial peritonitis, which could be improved by using ascitic fluid lactoferrin.

### Methods:

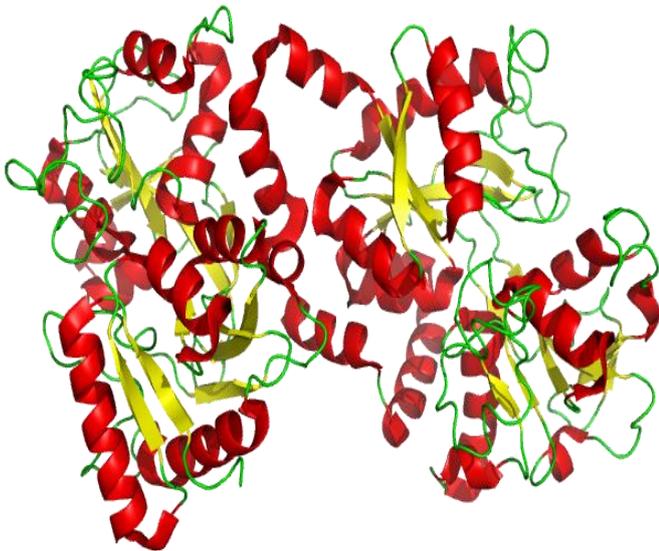
A search strategy has been performed to determine the related literature. Initially, the objective of review was identified: Diagnosis of spontaneous bacterial peritonitis could be improved by using ascitic fluid lactoferrin. Relevant keywords included: Ascitic

fluid lactoferrin, spontaneous bacterial peritonitis, more synonymous key words had been used.

These databases were searched for articles published in English in 3 data bases; PubMed – Google scholar and Science direct and Boolean operators (AND, OR, NOT) had been used such as Ascitic fluid lactoferrin AND spontaneous bacterial peritonitis OR polymorphonuclear leukocyte as well as in peer-reviewed articles between February 2003 and October 2021; a 18-year date range was selected, and no language limitations, and filtered in selected data basis for the last 18 years. Documents in a language apart from English have been excluded as sources for interpretation. Papers apart from main scientific studies had been excluded e.g. documents unavailable as total written text, conversation, conference abstract papers and dissertations.

### Lactoferrin:

Lactoferrin is a component of the human immune system. It has antibacterial properties (bactericide and fungicide) as well as an innate defensive mechanism, primarily at mucosal surfaces. Lactoferrin, in particular, has antibacterial properties for newborns. Heparin, polysaccharides, and DNA/RNA are among the ligands that lactoferrin interacts with, and the complexes they form reveal some of the biological tasks lactoferrin serves <sup>(4)</sup>.



**Figure (1):** Structure of lactoferrin <sup>(5)</sup>.

#### **Role:**

Lactoferrin is a molecule found in the body's innate immune system. For the most part, lactoferrin's principal function is to hold and transport iron ions, but it also has a variety of other properties and actions that make it useful in the treatment of a wide range of diseases <sup>(6)</sup>.

#### **Lactoferrin's enzyme activity:**

As lactoferrin is pyrimidine-specific, it hydrolyzes RNA and has the characteristics of secretory ribonucleases. Milk RNase blocks reverse transcription of retroviruses that cause breast cancer in mice by destroying their RNA genome. As a result, Parsi women in West India are three times more likely to develop breast cancer than the general population. This suggests that milk ribonucleases, in particular lactoferrin, may play a role in pathogenesis <sup>(7,8)</sup>.

#### **Ascitic fluid lactoferrin:**

Bovine milk and human breast milk contain lactoferrin <sup>(9)</sup>. This iron-binding protein is found in all of these secretions, as well as in the digestive juices and the mucous membranes <sup>(10)</sup>. Additionally, Lactoferrin is known to have anti-inflammatory and antioxidative capabilities, in addition to its cancer-fighting and antibacterial and antiviral activities <sup>(11)</sup>.

The production of lactoferrin by PMNs causes an increase in lactoferrin levels in the body during infection or inflammation. Lactoferrin levels grow during an infection or inflammatory illness <sup>(12)</sup>.

Potentially valid biomarkers for gastrointestinal sickness may be lactoferrin levels that are higher than normal <sup>(13)</sup>. Lactoferrin levels are higher in people with inflammatory bowel diseases like Crohn's disease and ulcerative colitis, as well as in people with colon cancer <sup>(14)</sup>.

Numerous studies in recent years have shown a link between elevated systemic inflammation and poor prognosis in various malignancies <sup>(15)</sup>. C-reactive protein levels and the neutrophil-lymphocyte ratio in patients

with hepatocellular carcinoma can be used to identify these systemic inflammatory responses <sup>(16)</sup>.

Lactoferrin levels in the ascitic fluid of people with cirrhosis-induced ascites are associated with an increased risk of developing hepatocellular carcinoma (HCC). Patients with severe liver disease are more likely to suffer from ascites. Patients with SBP, a clinical condition in which ascitic fluid is polluted, have no clear intra-abdominal etiology of peritonitis. PMN cells counts in ascitic fluid are used to diagnose SBP, with counts of 250 cells/mm<sup>3</sup> suggesting SBP, regardless of whether or not a positive blood or ascitic fluid culture is present. Cell count, culture, and lactoferrin levels in ascitic fluid samples were most acceptable for individuals with grade 2 or 3 ascites. However, because it is operator-dependent, it is prone to mistakes. If cells are lysed during transport to the laboratory, false negative results might also arise <sup>(17)</sup>.

**Parsi and colleagues** <sup>(18)</sup> found that SBP was diagnosed in cirrhotic patients by lactoferrin levels in their ascitic fluid. Only a few more studies have tested this study's conclusions. **Lee and colleagues** <sup>(17)</sup> concluded that the level of lactoferrin in ascitic fluid in patients with cirrhosis can be a helpful biomarker of SBP. In individuals without SBP, ascitic fluid lactoferrin concentrations beyond a certain threshold are a strong indicator of a patient's likelihood of developing hepatocellular carcinoma.

#### **Ascitic lactoferrin in diagnosis of SBP:**

As an alternative to PMN count, lactoferrin testing is a new biomarker for the identification of SBP. Activated PMN leukocytes release lactoferrin into the bloodstream, this lactoferrin is correlated with the flux of neutrophils in the bloodstream. Consequently, it was predicted to be effective in the detection of SBP as well <sup>(19)</sup>.

For SBP diagnosis, a single clinical trial was conducted in the early days of this test. SBP can be diagnosed by lactoferrin levels in ascitic fluid, with a sensitivity and specificity of 95% and 97%, respectively, in 218 ascitic fluid samples. In a study's quantitative lactoferrin assay, however, cannot currently be purchased. Lactoferrin concentration in the stool may now be measured at the bedside using qualitative and fast testing (to distinguish inflammatory from non-inflammatory bowel conditions). According to the researchers, it should be possible to create lactoferrin levels over a certain threshold for bedside diagnosis quickly and affordably. Lactoferrin in the ascitic fluid could serve as an early screening test for SBP in cirrhotic patients, according to the researchers <sup>(18)</sup>. SBP can be detected by lactoferrin in the ascitic fluid of individuals with cirrhosis, although this may be inaccurate since lysis of PMNs during transit to the laboratory may result in false negative results <sup>(20)</sup>.

**Hamed and colleagues** <sup>(21)</sup> found that patients with SBP have larger levels of lactoferrin in their ascitic fluid than those without SBP, according to a systematic evaluation of original studies <sup>(17, 18, and 20)</sup>. SBP should be suspected over a lactoferrin cut-off value established in four of the six original studies. For example, 3 of the 4 studies had cutoff values between 242 and 271 nanograms per milliliter <sup>(18, 20, and 22)</sup>. A far lower threshold, only 63 ng/ml, was reported in the fourth paper, with both lower specificity and no better specificity <sup>(17)</sup>. In the meta-analysis of these four studies, 207 ng/ml was found to be the most accurate cut-off point, with 91.5 percent specificity and a 93.8 percent overall accuracy.

**Hamed and colleagues** <sup>(21)</sup> concluded that ascites lactoferrin, can be used as a biomarker for spontaneous bacterial peritonitis.

## CONCLUSION

A biomarker for the existence of PMNs and the detection of SBP in cirrhotic individuals would be lactoferrin in the ascitic fluid. For bacterial peritonitis, lactoferrin is a promising and reliable biomarker that can be tested.

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