Study of Leucocyte Esterase Reagent Strips as a screening test for Spontaneous Bacterial Peritonitis

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Abstract: Background: Spontaneous bacterial peritonitis (S B P) is a severe and frequent complication of cirrhosis with a high mortality rate. A bacteriological laboratory is not always available for all departments admitting cirrhotic patients with ascitis. It follows that alternative methods for rapid diagnosis of SBP are an urgent requirement. **Objective**: This study was planned to compare between leucocyte esterase reagent strips as a bed side test and standard manual polymorphnuclear leucocytes (PMN) counting in the ascitic fluid as regards efficacy and rapidity in diagnosis of SBP. **Subjects & methods**: The study included 100 patients with liver cirrhosis resulting from chronic hepatitis C infection complicated by ascites and SBP. All patients were subjected to complete clinical examination, laboratory investigation that include CBC, PT, INR, LFT, s., creatinine and blood urea, pancreatic enzymes (amylase & lipase), ESR, tuberculin test, radiological investigations including CXR, pelvi-abdominal US and CT, in addition to specific investigations that include cytological, bacteriological and biochemical examination of ascitic fluid as well as examination of ascitic fluid by leucocyte esteras strips. **Results**: There was a highly statistically significance of leucocyte esterase reagent strips in diagnosis of SBP with high specificity 91.5%, sensitivity 83% and accuracy 88%. There was positive correlation (r = + 0.56) between ascitic fluid PMN counts and the corresponding result of leucocyte esterase reagent strip test which was statistically of high significance (*P* value= 0.000). **Conclusion**: It's concluded that the reagent strip testing of ascitic fluid is a very sensitive and specific method for diagnosis of SBP in cirrhotic patients with ascites. It can be used at the patient's bedside and is rapid, easy, inexpensive and results are available within a maximum of 120 seconds.
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1. Introduction

Cirrhosis is an irreversible alteration of the liver architecture. It consists of diffuse fibrosis of the hepatic parenchyma resulting in nodule formation[(1)].

The World Health Organization defined cirrhosis as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules which lack normal lobular organization[(2)].·

Liver cirrhosis is a disease found all over the world, affecting all races, ages, sexes. However, there are geographic differences regarding the most important factors as rate of alcohol consumption and frequency of viral? hepatitis [(3)].

Cirrhosis is often symptoms-free, autopsy examination suggest a prevalence of 4-10%. The incidence is about 240 per million inhabitants per year with high incidence of morbidity and mortality. Liver cirrhosis is the final stage of a hepatic disease which has generally run a chronic course for several years[(4)].

The mechanisms able to elicit and sustain liver fibrogenesis may be classified in three main groups: chronic activation of the wound healing reaction, oxidative stress, derangement of epithelial-mesenchymal interactions and epithelial-mesenchymal transition in cholangiopathies[(5)].

Ascites is the most common complication in decompensated cirrhotic patients. Approximately 50% of patients with compensated cirrhosis will develop ascites over a 10-years period[(6)].

Spontaneous Bacterial Peritonitis (SBP) is bacterial infection of the ascitic fluid without any intraabdominal source of infection[(7)].

Patients with cirrhosis and ascites show a higher susceptibility to bacterial infections mainly because of the inadequate defence mechanisms. The most frequent and the most severe one being SBP[(8)].

SBP occurs in 8-30% of hospitalized patients with ascites[(9)].

SBP pathogenesis in patients with cirrhosis is considered to be the main consequence of bacterial translocation (BT). The bacterial translocation is the process through which viable or non-viable bacteria and bacterial products (bacterial deoxyribonucleic acid (DNA) or endotoxins) cross the intestinal lumen and come into the mesenteric lymph nodes or extraintestinal. The BT is a disturbance of the equilibrium between the normal intestinal flora and the

organism, leading to an inflammatory reaction and finally producing infection. Bacterial translocation also is involved in increasing the hyperdynamic state of cirrhosis and in aggravation of haemostasis disorders[8].

There are some mechanisms that are being proposed to explain BT in cirrhosis: the intestinal bacterial overgrowth, the structural and functional alterations of the intestinal mucosal barrier and the deficiencies of the local immune response[10].

The intestinal bacterial overgrowth plays a key role in BT in cirrhosis and is the result of the delayed intestinal transit existing in these patients. It seems that the sympathoadrenal stimulation, increased nitric oxide (NO) synthesis and the oxidative stress of the mucosa are the main causes for decreased intestinal motility[10].

Besides, although normally in the small intestine there is a more reduced microbial density compared to that of the colon, in cirrhotic patients an increase of the colonization process of the small intestine with bacteria from the colon (approx.30-50%) is recorded [11].

In hepatic cirrhosis two processes that alter the intestinal mucosa barrier occur: increased mucosal permeability (especially in patients with sepsis) because of the mucosa oxidative stress, enterocyte mitochondria malfunctioning, endotoxaemia, increased nitric oxide (NO) and proinflammatory cytokine level and the mucosal structural changes. The latter include the intercellular spaces enlargement, vasodilatation, oedema, firbromuscular proliferation, decreased villi/crypts ratio, thickened muscularis mucosa and inflammation[12].

The structures that form the gut-associated lymphoid tissue (GALT) react to the presence of germs from the intestinal lumen by intraepithelial lymphocyte proliferation, germinative center appearance in the lymphoid follicles and in the lamina propria and an increase of the secreted immunoglobulin (Ig) level. In return, bacteria that form the commensal intestinal flora interact with the intestinal epithelium and can start up the primary immune response as well as the adaptative one[13].

In cirrhosis, because of the local and systemic immune deficiencies, the BT process is followed by bacteremia and ascitic fluid inoculation. If the ascitic fluid complement level is low, this will determine a low bactericidal activity and thus a higher risk of ***SBP*** [14].

For SBP diagnosis, the number of polymorpho-nuclear leucocytes (PMN) from the ascitic fluid obtained by paracentesis must exceed 250 cells/mm^3 and from bacteriological cultures only one germ must be isolated [15].

Culture-negative neutrocytic ascites (probable SBP) exists when the ascitic fluid culture are negative yet the neutrophil (PMN) count is >250 cells/mm^3. This may happen in as many as 50% of patients with SBP and may not actually represent a distinctly different disease entity. It may be the result of poor culturing techniques or late-stage resolving infection[16].

Bacterascites exists when a positive culture coexists with a non elevated ascites PMN count. Although this often may be the result of contamination of bacterial cultures, this may represent an early form of the disease. All patients described that eventually developed SBP were symptomatic, making this a valuable aid in establishing a diagnosis [17].

However, because of the organization of facilities in many hospitals, a bacteriological laboratory is not always available for all departments admitting cirrhotic patients with ascites. It follows that alternative methods for rapid diagnosis of SBP are an urgent requirement[18] .

Use of reagent strip testing for leucocyte esterase has been proposed to reduce the time from paracentesis to a presumptive diagnosis of SBP from a few hours to a few seconds[18].

The aim of this study is to compare between leucocyte esterase reagent strips as a bed side test and standared manual PMN counting in the ascitic fluid as regards efficacy and rapidity in diagnosis of SBP.

2.SUBJECTS AND METHODS

This study was carried out in intensive care unit of Internal Medicine Department, Zagazig University Hospital.

The study was conducted on 100 patients with liver cirrhosis resulting from chronic hepatitis C infection complicated by ascites and spontaneous bacterial peritonitis (SBP) which diagnosed by:

*__Clinical presentation:__ Fever, generalized abdominal pain and tenderness.

*__Laboratory investigation:__ (PMN in ascitic fluid > 250/mL).

Exclusion Criteria:

I. Ascites due to renal, cardiac, tuberculous, malignant pathology and pancreatic ascites.

II. Secondary peritonitis.

III. Patients with focal lesion or hemoperitoneum complicating hepatocellular carcinoma were also excluded.

All patients were subjected to the following:

I- Full medical history and physical examination:

II- Laboratory investigations:

1. Complete blood count (CBC).
2. Prothrombin time (PT). Normal PT was regarded as 12 seconds and International Normalized Ratio (INR).
3. Liver functions tests (total plasma proteins, serum albumin, alanine amino transaminase (ALT),

aspartate aminotransferase (AST), total and direct serum bilirubin, and alkaline phosphatase.
4. Kidney function test [serum creatinine, blood urea nitrogen (BUN)].
5. Pancreatic enzymes (amylase &lipase).
6. Erythrocyte Sedimentation Rate (ESR).
7. Tuberculin test.

III- Radiological investigations:

1 - Chest x-ray
2- Abdominal & Pelvic ultrasonography
3- Computed tomography Scanning of the abdomen and pelvis: Abdominal ultrasonographic examination and Computed Tomography scanning were done in fasting state evaluating:
*The liver for size, echo pattern and presence or absence of focal lesions.
*Presence or absence of hepatic periportal fibrosis.
*The spleen for size, hilar varices and dilatation of the splenic vien.
*Presence of ascites.
*Portal vein diameter (normally regarded as 9-12 mm) and presence or absence of thrombosis.
*Abdominal lymph node enlargement (para aortic & porta hepatis).
*The ovary (masses were excluded from the study)

IV-Cytological, Bacteriological, and biochemical examination of ascitic fluid.

V-Examination of ascitic fluid by leukocyte esterase strips.

Specimen collection:

The site of an ascitic tap is away from the midline, at the point of maximal dullness, and ideally in the left iliac fossa, two fingerbreadths medial and two ventral to the anterior superior iliac spine ("Runyon's spot")[19]. Equipment required for the tap comprises: 10-mL syringe; 1.5-inch, 22-gauge metal (or 18-gauge) needle; pack of sterile gloves and a galipot with skin disinfectant[20].

Data processing and analysis:

*The collected data were reviewed and coded.
*SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.
*Quantitative data were represented as arithmetic means and standard deviations (means ± SD); the "t test" was used for comparison between two groups and Mann-Whitney U test (for not normally distributed data)
*Qualitative data were represented as frequencies and percents, Chi square test (x^2) was carried out for calculating significant relations between the groups.
*The results were considered statistically significant when the significant probability was less than 5 % ($p < 0.05$).
*Exact 95% confidence interval (C.I) for each statistic was calculated from the binominal distribution.

***Sensitivity:** was defined as the proportion of patients with a positive reagent strip divided by the number of those with SBP diagnosed by criteria previously defined.
***Specificity:** was defined as the proportion of patients with a negative reagent strip divided by the total number of patients without SBP.
***Positive predictive value (PPV):** was defined as the proportion of patients with a true-positive reagent strip divided by the total number of patients with a positive reagent strip.
***Negative predictive value (NPV):** was defined as the proportion of true-negative reagent strips divided by the total number of patients with a negative reagent strip.
***Accuracy** was defined by dividing the sum of the true positives and true negatives by the total number of samples evaluated.

Ethical consideration:

The consent of patients who are studying them was taken and the confidentiality of consumers' data were kept and used only for this study.

3. Rusults

Table (1): Comparison between patients with SBP and those without SBP as regard to age, sex and Child- Paugh classification: There is no statistical significant difference between both groups as regard age, sex and Child-Paugh classification.

Table (2): Distribution of the study population according to leukocyte estrase reagent strips result (n =100): This table shows results of leukocyte esterase reagent strips in which 56% test negative and 25% test +3.

Table (3): Distribution of the study population according to SBP which diagnosed laboratory by (PMN ≥250/ml) (n. = 100): This table shows results of S.B.P diagnosed laboratory by (PMN>250/mL) in which 41% positive (+ ve) and 59% negative (- ve).

Table (4): Validity scores of leukocyte estrase reagent strips in diagnosis of SBP (PMN ≥ 250/ ml) using cut off value ≥ +2 of the strips: It shows that:
True positive cases = 34
False positive cases = 5
True negative cases = 54
False negative cases = 7
Total cases =100
So the validity of the test is:
Sensitivity = 34/41* 100- 83%.
Specificity = 54/59* 100= 91.5%.
Positive predictive value (PPV) = 34/39* 100=87.2%.
Negative predictive value (NPV) = 54/61* 100- 88.5%.
Accuracy = 34 + 54/100* 100 = 88%.

Table (5): Sensitivity, Specificity, Positive predictive value and Accuracy for the reagent strips to

diagnose correctly SBP: This table shown validity and accuracy of the reagent strips to diagnose correctly SPB.

Table (6) and Fig (1): Correlation between ascitic fluid PMN counts and the corresponding result of leucocyte esterase reagent strip test: There is positive correlation (r = +0.56) between ascitic fluid polymorphonuclear (PMN) counts and the corresponding result of leukocyte esterase reagent strip test which is statistically high significant (*p* value = 0.000).

Table (7): Culture of SBP positive cases: Shows that the common organism of SBP was *E. coli* (34.14%) and Klebsiella (21.95%).

Table (1): Comparison between patients with SBP and those without SBP as regard to age, sex and Child-Paugh classification

Variable	SBP(n.=41)	Non-SBP (n.= 59)	Significant test	*P* value
1- Age (years) - mean ± SD	54.61±8.24	54.85±9.7	0.128*	0.89
2-Sex				
- male	29	44	0.18**	0.67
- female	12	15		
3-Child-Paugh Classification				
- A	1	7		
- B	18	30	4.403**	0.11
- C	22	22		

*** T test. ** X^2 (Chi square test).**

Table (2): Distribution of the study population according to leukocyte esterase reagent strips results (n. =100).

Strip result	N.	%
0 (negative)	56	56%
+ 1	5	5%
+ 2	14	14%
+ 3	25	25%

Table (3): Distribution of the study population according to S.B.P which diagnosed laboratory by (PMN ≥ 250/mL) (n. =100)

S.B.P diagnosed laboratory (PMN > 250/mL)	N.	%
- ve	59	59%
+ ve	41	41%

Table (4): Validity scores of the leukocyte esterase reagent strips in the diagnosis of spontaneous bacterial peritonitis (PMN ≥ 250/mL) using cut off value ≥ + 2 of the strips.

Leukocyte esterase reagent strips	Spontaneous bacterial peritonitis		Total
	Positive	Negative	
Test +ve	34	5	39
Test -ve	7	54	61
Total	41	59	100

Table (5): Sensitivity, Specificity, Positive predictive value (PPV), Negative predictive value (NPV) and Accuracy for the reagent strips to diagnose correctly spontaneous bacterial peritonitis (SBP)

Variable	Value	95% C.I
Sensitivity	0.83	0.75-0.91
Specificity	0.915	0.89-0.95
Positive predictive value (PPV)	0.87	0.84-0.9
Negative predictive value (NPV)	0.885	0.86-0.92
Accuracy	0.88	0.85-0.91

Table (6): Correlation between ascitic fluid polymorphonuclear (PMN) counts and the corresponding result of leukocyte esterase reagent strip test

Variable	Pearson correlation (r)	*P* value
Polymorphonuclear (PMN)	0.56	0.000
Test	1.000	0.000

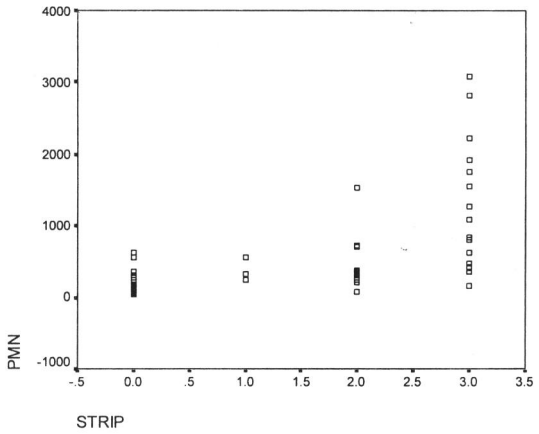

Fig. (1): Correlation between ascitic fluid polymorphonuclear (PMN) counts and the corresponding result of leukocyte esterase reagent strip tests

Table (7): Culture of spontaneous bacterial peritonitis positive cases

Culture result	N. = 41	%
Negative	3	7.31%
Staph. coagulase Negative	4	9.8%
E. coli	14	34.14%
Klebsiella	9	21.95%
Proteus	5	12.2%
Citrobacter	6	14.6

4. Discussion

Cirrhosis which is considered the third leading cause of death after cardiovascular disease and cancer in the Western world results in major complications such as portal hypertension with variceal bleeding,

ascites, or liver failure leading to renal failure and coma [21].

It has been said that cirrhosis is the most common form of immunodeficiency, exceeding even AIDS. Infectious complications in cirrhotic patients can cause severe morbidity and mortality[22].

Spontaneous bacterial peritonitis is a severe and frequent complication of cirrhosis with a high mortality rate. Spontaneous bacterial peritonitis is probably related to several impaired defense mechanisms, such as depressed reticuloendothelial system phagocytic activity, leukocyte dysfunction, reduced serum complement, and low bacterial activity of ascitic fluid [23].

Use of reagent strip testing for leucocyte esterase has been proposed to reduce the time from paracentesis to a presumptive diagnosis of SBP from a few hours to a few Seconds [18].

The test is based on the esterase activity of granulocytes. 3-Hydroxy-5-phenyl-pyrrole esterified with an amino acid is used as the substrate. Hydrolysis of this ester by the esterase releases 3- hydroxy-5-phenyl-pyrrole, which in turn reacts with a suitable diazonium salt, yielding a violet azo dye, the intensity of which correlates to the leukocyte count [24].

The aim of this study is to compare between leucocyte esterase reagent strips as a bed side test and standard manual PMN counting in the ascitic fluid as regarding efficacy and rapidity in diagnosis of SBP. The study was conducted on 100 patients with liver cirrhosis complicated by ascites and spontaneous bacterial peritonitis (SBP).

In this work, the test of ascitic fluid by leukocyte esterase reagent strips showed that 39 patients were positive (+ve) and 61 patients were (-ve) , while laboratory examination of ascitic fluid showed that 41 patients were (+ve) and 59 patients were negative (-ve) with Specificity =91.5% and Sensitivity = 83%

These results were in agreement with that of **Castellote *et al.,*** [25], who demonstrated sensitivity (96%) and specificity (89%) for detecting SBP in cirrhotic patients with ascites. Also, these results were in consistent with that of **Vanbiervliet *et al.,*** [26] study that showed the Multistix 8SG rapid urine screening test had 100% sensitivity and specificity for SBP diagnosis.

In another study, the reagent Combur-2 test® LN, was tested and showed a sensitivity of 89% and a specificity of 100% [27]. In the same direction, **Sithara *et al.,*** [28] showed results of LER strip using the more stringent purple-color cut off to diagnose SBP had a sensitivity of 92% and specificity of 100%.

In contrast, **Nousbaum *et al.,*** [29] study showed that sensitivity was only 45.3%. Several explanations are possible for this poor sensitivity. First, published studies were limited to a small number of patients with SBP. Second, the strip was initially designed for detection of urinary tract infections in which the number of leukocytes is significantly higher than in SBP.

In this work, Positive predictive value (PPV) and negative predictive value (NPV) of leukocyte esterase reagent strips in the diagnosis of S.B.P were 87.2%.and 88.5%. This findings were in accordance with that of **Tarsila *et al.,*** [30] who showed that positive and negative predictive value were 91% and 98%. With a positive reagent strip results taken as grade 2 or more.

This study showed the accuracy of the reagent strips to diagnose correctly spontaneous bacterial peritonitis (SBP) was 88%. In the same context, **L'opez *et al.,*** [31] who studied a group of non selected paracentesis performed on a cohort of cirrhotic patients, at admission, when an SBP was suspected or was clinically indicated, by use of a reagent strip for leukocyte esterase designed for the testing of urine (Aution sticks; A. Menarini Diagnostics, Firenze, Italy), the accuracy of the reagent strips was 0.91 (0.87-0.94).

In this study, the commonest causative agents isolated from infected ascetic fluid in our stud^ were *Escherichia coli* (34.14%), Klebsiella spp. (21.95%), Citrobacter (14.6%), Proteus (12.2%).

This results were in consistent with that of **Koulaouzidis *et al.,*** [32] who showed that the commonest causative agents isolated from infected ascitic fluid were *Escherichia coli* (70%), Klebsiella spp. (10%), Proteus spp. and *Enterococcus faecalis* (4% each), Pseudomonas spp. (2%) and others (6%). This difference in prevalence might be explained by the difference in study size.

This study showed that there was positive correlation (r= +0.56) between ascitic fluid polymorphonuclear (PMN) counts and the corresponding result of leukocyte esterase reagent strip test which was statistically high significant (*p* value = 0.000)

Although, this results were in consistent with that of **Castellote *et al.,*** [33] study in which a group of non selected cirrhotic patients were undergone diagnostic paracentesis performed on a cohort of cirrhotic patients were studied at admission, there was a very good correlation between the reagent strip test result and the PMN count, using Aution sticks (Arkray Inc., Edina, Minnesota,USA) , it was against with that of **Daniel *et al.,*** [34] who reported that there was a lack of correlation between the degree of reagent strip positivity and the ascitic PMN counting (Bedside leucocyte esterase reagent strips with spectro-photometric analysis to rapidly exclude spontaneous bacterial peritonitis [35, 36].

This difference in this result may be explained by the reagent strip results were read spectrophotometrically using the clinitek status, thus removing operator subjectivity or indeed error (if colour blind). This removes interobserver variability from the diagnostic algorithm. Another explanation that in our study we selected highly suspected patients with SBP from intensive care unit of internal medicine department while others showed non selected cirrhotic patients for diagnosis. In addition, these strips have only been validated for urine by the manufacturers and numerous factors in ascites, not present in urine, could affect that colorimetric reaction[37].

In summary,

There was a highly statistically significance of leukocyte esterase reagent strips in diagnosis of SBP with highly Specificity 91.5%, Sensitivity 83% and Accuracy 88%.

There was positive correlation (r= +0.56) between ascitic fluid polymorphonuclear (PMN) counts and the corresponding result of leukocyte esterase reagent strip test which was statistically of high significance (*p* value =0.000).

Conclusion:

It's concluded from this study that the reagent strip testing of ascitic fluid is a very sensitive and specific method for diagnosis of SBP in cirrhotic patients with ascites. It can be used everywhere at the patient's bedside and is rapid, easy to use, inexpensive and results are available within a maximum of 120 seconds. A positive result should be an indication for empirical antibiotic therapy, and a negative result excludes SBP and may be useful as a screening test in patients on large-volume paracentesis.

Recommendation:

- There must be much more work about the leukocyte esterase reagent strips as a bed side test in cirrhotic patients with ascites.
- The work must include the efficacy and the rapidity of leukocyte esterase reagent strips for the early detection of the possibility of developing SEP.

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