Are reagent strips useful for the diagnosis of spontaneous bacterial peritonitis?

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Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication of cirrhosis [1-3]. The prognosis of SBP has been improved by the use of antibiotics with high peritoneal diffusion, low nephrotoxicity, and by the prophylactic use of antibiotics in high risk groups of patients [4]. Improved survival may also be explained by more rapid diagnosis and treatment thus preventing severe sepsis and septic shock, a condition well known for its frequently fatal outcome [5]. Diagnosis of SBP is based upon a polymorphonuclear neutrophil (PMN) count that is at least 250/µL with or without positive culture [1]. However in some instances, it is difficult to obtain an ascitic cell count within a few hours, and the clinician may decide to begin empiric antibiotic administration based on clinical or biological signs suggesting infection. Indeed, Runyon [6] suggested that the patient’s outcome may be hindered by unacceptable delays in diagnosis depending on the rapid availability of PMN count testing results. Surrogate markers for rapid diagnosis of SBP are thus urgently required.

The use of urinary reagent strips has been recently proposed for a rapid diagnosis of SBP. The urinary strips identify leukocytes by detecting their esterase activity via a colorimetric reaction [7, 8]. The use of Multistix® strips has been tested for the diagnosis of bacterial meningitis [9], pleural infection [10], synovial infection [11], and peritoneal infection in dialysis patients [12, 13]. It has been suggested that the use of a reagent strip could be promising for the diagnosis of SBP. The first study was performed in France by Vanbiervliet et al. [14]. In this study involving 72 consecutive cirrhotic patients, the authors tested the diagnostic performance of Multistix 8 SG®, the most frequently used urinary reagent strip in France. Nine patients had SBP and the sensitivity and specificity of this strip for the diagnosis of SBP were 100% and 100% respectively [14]. Since this study published in 2002 several studies from France, Italy and the United States have confirmed these results in the past 3 years. The sensitivity of urinary reagent strips for the diagnosis of SBP ranged between 85% and 100% and the specificity of these strips ranged between 98 and 100% [15-20].

A closer look at the results of all these studies had revealed a heterogeneity in the number of patients studied (31 to 228), the severity of cirrhotic patients included, the number of samples tested (72 to 245) and more important marked differences in the number of episodes of SBP observed ranging from 9 to 52 [16, 17]. In addition, the reagent strips used are not always the same and the diagnostic performances of the different urinary strips used may be different [16-18]. The results of Multistix reagent strips (either 8 SG® or 10 SG®) have been studied most often [14, 17-20]. In studies published as peer-review articles, the sensitivity of Multistix strips (either 8 SG® or 10 SG®) for the diagnosis of SBP ranged from 64.7% [18] to 100% [14, 17] whereas the specificity was better, ranging from 99% [15] to 100% [14, 17]. Although the positive predictive value of Multistix® for the diagnosis of SBP ranged from 91.7% [18] to 100% [14, 17], it was only 42% in the study of Wisniewski et al. [20] which considered a “trace” result as positive. Other reagent strips (see below) may have better diagnostic results [18].

Thus, the usefulness of reagent strips for the diagnosis of SBP has been clearly documented. The publication in this issue of Gastroentérologie Clinique et Biologique of the study of Campillo et al. [21], a large study involving 443 paracentesis in 116 patients with 46 SBP, provides important new results in this area. In this study: 1) the authors found a high prevalence of gram-positive pathogens and enterobacteriaceae responsible for 36% and 21% of SBP episodes and 71% and 29% of symptomatic bacterascites respectively confirming the specificity of ascitic infections in their centre [22]; 2) The Comb turbostest® (a variant of the Nephur test®) provides better results than the Multistix 8 SG® with a sensitivity of 80.4% and 69.6% respectively at grade 1 (15 leucocytes/mm³) for the diagnosis of SBP, confirming the better performance of the former as recently shown by Sapey et al. [18] with the Nephur test®; 3) grade 2 positivity (70 leucocytes/mm³) increased specificity and the positive predictive value for both strips; 4) the most important finding in their study is the poor performance of both strips when polymorphonuclear cell count was below 1000/mm³ as already reported by Butani et al. [15] as well as the failure of reagent strips in cases of symptomatic bacterascites, with a sensitivity of 22.4% with the Multistix 8 SG® and 44.4% with the Comb turbostest® respectively in this setting. Although these results are important, we must keep in mind that their series may have a specific bias because patients followed in their center are at very high risk of developing SBP [23], since they have been hospitalized for several days or weeks (46.6 ± 29.9 days), have severe liver failure (median Child-Pugh score 10.7 ± 1.8; bilirubin 108 ± 115 µmol/l) and 61% of them have ascitic protein level below 15 g/L. Diagnostic paracenteses were probably performed at the beginning of infection which could explain a loss in sensitivity of the reagent strips. What conclusions can now be drawn, and what is the role of reagents strips for the diagnosis of SBP in cirrhotic patients?

On this topic, additional data is available from the French prospective multicenter study conducted with investigators of the...
“Club Francophone pour l’Etude de l’Hypertension Portale” and the “Association Nationale des Hépato-Gastroentérologues des Hôpitaux Généraux de France” [24]. This large study included 2123 paracenteses performed in 1041 patients from 70 centers as well as 117 ascites specimen (in 91 patients) with criteria of SBP. The PMN count ranged from 250/μL to 34 000/μL. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of the Multistix® 8 SG for the diagnosis of SBP, when considering a reagent strip positive with the grade 3 (125 leucocytes/mm³, that is the closest of the threshold of 250 PMN/mm³ defining SBP) were 45.3, 99.2, 77.9 and 96.9% respectively. However if grade 1 positivity is taken into account as in the study by Campillo et al. [21] the sensitivity of the strip was 62% making our results similar to those of Campillo et al. [21]. However, the sensitivity of the Multistix 8 SG® test was low in this multicenter prospective study as well as in the study of Campillo et al. [21] and Sapey et al. [18] and it is questionable whether grade 1 (15 leucocytes/mm³) should be considered a positive result.

However, the French multicenter study confirmed that the specificity of the Multistix 8 SG® reagent strip is very high in the diagnosis of spontaneous bacterial peritonitis.

What are the possible explanations for this poor sensitivity? First except for Castellote et al. [16] and Campillo et al. [21] all published studies were limited to a small number of patients with SBP (n < 20). According to the 95% confidence intervals, in a larger population of patients with SBP a high rate of false negative tests could be expected [18]. In the study performed by Butani et al. [15], two of the samples with a negative leucocyte esterase test had the two lowest absolute PMN values, 1.088 and 368 PMN/μL respectively. The authors suggested that the test was less sensitive in a weakly positive setting. In our study, as in the study by Campillo et al. [21], the large number of samples with low PMN values may explain the lowest sensitivity reported so far.

Second, other reagent strips may be more accurate. Castellote et al. [16] used Autions sticks manufactured in Italy and they observed 89% sensitivity. Sapey et al. [18] compared the Multistix 10 SG® and the Nephur test® and showed that Nephur-test® was more sensitive (88.2% vs 64.7%). The Combustest®, which is a modified version of the Nephur test®, has also been recently compared with the Multistix® in two studies [17, 21]. The sensitivity of the tests were identical in the first study [18] and the Combustest® was more sensitive than the Multistix® 8 test in the study by Campillo et al. [21] when a threshold of grade 2 on the colorimetric scale was used (63.0 vs 45.7%).

Third, the Multistix strip was designed for the detection of urinary tract infections where the number of leucocytes is significantly higher than in SBP. In SBP, infection is associated with a high morbidity and a high mortality rate. Therefore antibiotic administration should not be delayed based on a negative test result. The strip may help the clinician when the test is positive, as the specificity of the test is very high. Indeed, in our study and other published studies, the specificity of the test was 99.2% and ranges in the literature from 99 to 100% [14, 16, 17]. Conversely, a negative result cannot exclude the diagnosis of SBP, particularly in symptomatic patients, where the sensitivity ranges from 48.1% to 69.6% [21] with the Multistix SGG®.

Finally, concerning the severity of SBP, the rate of false negative results is high for all reagent strips [18, 21, 24]. These tests can certainly help the clinician when a cell count is not available within a few hours and/or if the result of the test is positive. Reagent strips could be useful in developing countries without sufficient resources; the cost of the strip is only 0.15 euro. In addition, the prevalence of SBP depends on the population. Indeed, it has been shown that the prevalence of SBP is low in ambulatory asymptomatic patients where therapeutically paracenteses are performed for refractory ascites ranging from 0 to 2% [25-27]. The results of the published studies including that reported by Campillo et al. [21] published in this issue of the review do not support the systematic replacement of standard ascites fluid analyses by the use of reagent strips for the diagnosis of SBP.

REFERENCES

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