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Sensitivity of a bedside reagent strip for the detection of spontaneous bacterial peritonitis in ED patients with ascites

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ABSTRACT

Study objective: To determine the sensitivity of a highly sensitive bedside leukocyte esterase reagent strip (RS) for detection of spontaneous bacterial peritonitis (SBP) in emergency department (ED) ascites patients undergoing paracentesis.

Methods: We conducted a prospective, observational cohort study of ED ascites patients undergoing paracentesis at two academic facilities. Two practitioners, blinded to each other's results, did a bedside RS analysis of the peritoneal fluid in each patient and documented the RS reading at 3-min according to manufacturer-specified colorimetric strip reading as either "negative", "trace", "small", or "large". The primary outcome measure was sensitivity of the RS strip for SBP (absolute neutrophil count $\geq$ 250 cells/mm^3) at the "trace" threshold (positive equals trace or greater).

Results: There were 330 cases enrolled, with 635 fluid analyses performed. Of these, 40 fluid samples had SBP (6%). Bedside RS had a sensitivity, specificity, positive predictive value, and negative predictive value of 95% (95% CI 82%–99%), 48% (95% CI 44%–52%), 11% (95% CI 10%–11%), and 99% (95% CI 97%–99%) respectively at the "trace" threshold for the detection of SBP.

Conclusion: Bedside use of the RS in ED ascites patients demonstrated high sensitivity for SBP. Given the wide confidence intervals, we cannot currently recommend it as a stand-alone test. We recommend further study with a larger number of SBP patients, potentially combining a negative RS result with low clinical suspicion to effectively rule out SBP without formal laboratory analysis.

1. Introduction

1.1. Background and importance

Diagnostic paracentesis is an important procedure in evaluating for spontaneous bacterial peritonitis (SBP) in the patient with ascites. SBP, even with antibiotic treatment, has a mortality between 8%–28% [1,2]. The accepted standard of care for diagnosis of SBP is a peritoneal fluid absolute neutrophil count (ANC) >250 cells/mm^3, regardless of culture growth, as it is difficult to culture bacteria even in the presence of obvious infection [3]. This requires a cell count and differential be performed, which can be time-consuming in a busy emergency department (ED), and require either an automated cell counter or a 24/7 technician for manual cell counts, both of which may be too costly in institutions with lower volumes or in developing countries.

Two previous ED studies have examined whether clinical characteristics commonly ascribed to SBP (i.e. fever, emesis, abdominal pain), peritoneal fluid appearance, or physician clinical suspicion for SBP are adequate for ruling out SBP without the need for fluid laboratory analysis. These studies showed none of these were adequate for ruling out SBP, with the physician clinical suspicion of SBP (using clinical characteristics and peritoneal fluid appearance, but without fluid analysis) having a sensitivity of 42%–76% for the detection of SBP [4,5].

Urine reagent strips using the leukocyte esterase method have been examined as a method to rapidly detect SBP at bedside in peritoneal fluid of cirrhotic patients. While these strips have demonstrated specificity as high as 98%, allowing for the possibility of more rapid treatment of SBP patients, the sensitivity is too

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low and variable (31%–100%) to be useful in the rapid rule out of SBP [6,7].

A more highly sensitive bedside reagent strip (RS) has been developed and is in use for peritoneal dialysis patients. This RS was examined in a lab model of SBP, and found to have a sensitivity of 100% in the detection of SBP [8]. This prompted a study involving 1402 paracenteses in which the RS was found to have a sensitivity of 92% at the "trace" threshold. However, this was performed in a broad range of inpatient and outpatient populations and did not examine an ED population [9]. As routine peritoneal fluid analysis adds significant cost and length of stay, if it was shown that the sensitivity of RS for the detection of SBP was high in ED patients, one could safely omit the laboratory analysis after paracentesis.

1.2. Goals of this investigation

The aim of this study, then, is to prospectively determine if bedside RS analysis has sufficient sensitivity to reliably exclude the diagnosis of SBP, thus obviating the need for laboratory fluid analysis.

2. Methods

2.1. Study design and setting

This was a prospective, observational cohort study conducted in ascites patients undergoing ED paracentesis. The study was conducted in two academic EDs with largely underserved populations, and a combined census of approximately 165,000 patients annually. Both EDs have emergency medicine residency programs staffed with board-certified faculty emergency physicians, emergency medicine residents, nurse practitioners and physician assistants.

2.2. Selection of participants

ED ascites patients receiving paracentesis and fluid analysis were enrolled in the study. There were no exclusion criteria. Enrollment of a convenience sample of patients occurred 24 h a day during all days of the week. Patients were enrolled between April 2016 and January 2018.

The study was approved by the institutional review boards at each facility. Patient consent was waived at one facility and required at another. At the facility requiring study consent, patients had consent documented prior to paracentesis.

2.3. Intervention and measurements

RS analysis was done using the Periscreen (Serim Corporation) strip. Strips were stored in the sealed bottle at ED room temperature. While providers did not receive formal training, instructions on how to apply fluid to the strip were on the enrollment form. The strip had the colorimetric portion immersed in peritoneal fluid and removed directly after and placed flat while timer was started; streaming of the fluid was not performed.

Patients received a paracentesis by an ED provider. Two providers, prior to sending fluid for lab analysis, did peritoneal fluid RS analysis at bedside and were blinded to each other's results. A timer was set for 3-minutes and the provider documented the manufacturer-specified RS reading of either "negative", "trace", "small", or "large" at 3-min (Fig. 1). Fluid appearance and whether unblinding of results had occurred were also documented. Fluid was sent for cell count and differential in all patients with optional Gram stain/culture.

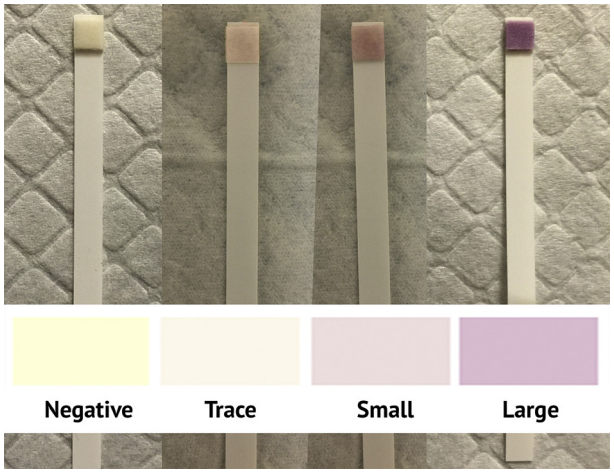

Fig. 1. Highly-sensitive leukocyte esterase reagent strips (Periscreen) demonstrating "negative", "trace", "small", and "large" colorimetric results.

Chart review examining patient characteristics was performed by two study coordinators who received standardized training and used a standardized abstraction spreadsheet. They were not blinded to the purpose of the study, but they did not have access to the RS analysis readings when doing chart review. Ten patients were randomly selected and had a separate study investigator perform chart review to determine interrater agreement on the different variables.

2.4. Definitions

SBP was defined as an absolute neutrophil count (ANC) $\geq$ 250 cells/mm^3. For cases of bloody or traumatic paracentesis, one neutrophil was subtracted for every 250 red blood cells/mm [3,10]. Fluid culture was positive if there was growth of a pathogenic organism according to a pre-defined list. RS analysis was considered positive for SBP at the "trace" threshold if the RS read "trace", "small", or "large". Interrater agreement was achieved at the "trace" threshold if both were read as "trace", "small", or "large", or both "negative", or "exact" positive if both were read the exact same.

2.5. Outcomes

The primary outcome measure was sensitivity of the 3-minute RS reading for the detection of SBP at the "trace" threshold. Secondary outcome measures included interrater agreement of RS readings between the 2 providers at the "exact" and "trace" thresholds.

2.6. Analysis

Sensitivity, specificity, and 95% confidence intervals were calculated using online calculators at http://vassarstats.net/clin1.html.

Sample size calculation was done in the following way: With a goal sensitivity of the reagent strip reaching 100% for the detection of SBP, and the lower limit of the 95% confidence interval at 90%, 35 patients with SBP must be enrolled (http://www.swogstat.org/stat/public/binomial_conf.htm). From previous studies, we estimated the prevalence of SBP to be 12% in ED ascites patients [4,5]. Thus, the necessary sample size to enroll 35 SBP patients would be 292. We set an enrollment goal of 330 patients, to account for incomplete data or a lower than anticipated prevalence of SBP.

3. Results

3.1. Characteristics of study subjects

There were 282 patients who had 330 paracenteses enrolled between April 2016–January 2018. In 10 paracenteses, there was either no ANC data or RS reading available. Of the remaining 320 paracenteses, there were 315 with RS readings from 2 providers, and 5 with only one provider RS reading available, for a total of 635 total peritoneal fluid assessments. Patient characteristics are listed in Table 1. End-stage liver disease was an etiology for ascites in 95% of patients. In a five-month audit, 35/84 (42%) paracenteses that occurred in both EDs were enrolled in the study.

3.2. Reagent strip readings

Table 2 details the results of the RS readings. Using the "trace" threshold, 45% of the fluid samples were considered negative for SBP by RS analysis. Interrater agreement of the 3-min RS reading was 71% and 78% at the "exact", and "trace" thresholds, respectively. Of the 5 patients with only one provider RS reading available, none had SBP.

Table 3
RS test performance.

		Final diagnosis	
RS test result		SBP	No SBP
"Trace" threshold	Positive	38	309
	Negative	2	286
Sensitivity (95% CI)	95% (82%–99%)		
Specificity (95% CI)	48% (44%–52%)		
Positive predictive value (95% CI)	11% (10%–11%)		
Negative predictive value (95% CI)	99% (97%–99%)		

RS, reagent strip; CI, confidence interval.

3.3. Main results

The primary outcome measure, sensitivity of the 3-min RS reading for detection of SBP at the "trace" threshold, was 95% (95% CI 82%–99%) (Table 3).

4. Discussion

Lack of equipment and specialized personnel in smaller hospitals, and the delay associated with peritoneal fluid testing for

Table 1
Patient and vital sign characteristics.

		All (n = 282)	SBP (n = 20)	No SBP (n = 262)
Patient characteristics	Male (%), Female (%)	198 (70): 84 (30)	17 (85): 3 (15)	181 (69): 81 (31)
	Mean age, years (S.D.)	55.5 (9.7)	54.2 (10.7)	55.5 (9.6)
	Admitted to hospital, n (%)	101 (36)	16 (80)	85 (32)
Etiology ascites[a], n (%)	Cirrhosis, alcoholic	178 (63)	10 (50)	168 (64)
	Cirrhosis, hepatitis C	108 (38)	6 (30)	102 (36)
	Cirrhosis, other causes	53 (19)	5 (25)	48 (17)
	Peritoneal carcinomatosis	10 (4)	1 (5)	9 (3)
	Renal failure	15 (5)	1 (5)	14 (5)
	Congestive heart failure	9 (3)	0 (0)	9 (3)
	Other	5 (2)	0 (0)	5 (2)
Vital signs[b], n (%)	Temperature ≥ 38-degrees C	8 (2)	4 (20)	4 (1)
	Temperature < 36-degrees C	14 (4)	2 (10)	12 (4)
	Pulse ≥ 100 bpm	130 (39)	9 (45)	121 (39)
	Systolic BP < 90 mm Hg	26 (8)	5 (25)	21 (7)

[a] Patients could have more than one etiology for ascites.
[b] Denominator of 330 total and 20 SBP cases.

Table 2
Fluid characteristics, RS readings, and RS sensitivity and specificity calculations.

		All	SBP	No SBP
Fluid characteristics				
Description, n (%)[a]	Straw	360	5	355
	Hazy	128	11	117
	Cloudy	60	11	49
	Bloody	57	6	51
	Other	18	3	15
Lab analysis[b]	% Neutrophils (IQR)	17% (16)	72% (11)	13% (13)
	Mean ANC, mm^3 (IQR) Mean ANC, mm^3 (IQR)	263 (30)	3863 (5461)	22 (19)
	Gram stain positive, n (%)	2 (0.6%)	0 (0%)	2 (0.6%)
	Culture positive, n (%)	11 (3%)	6 (30%)	5 (2%)
RS analysis				
3-Minute reading, n (%)	Negative	289 (45)	2 (1)	287 (45)
	Trace	233 (37)	5 (1)	228 (36)
	Small	69 (11)	7 (1)	62 (10)
	Large	36 (6)	24 (4)	12 (2)
	Bloody/other	8 (1)	2 (1)	6 (1)
Performed reading, n (%)[c]	Attending	162 (34)	12 (2)	150 (31)
	Resident	312 (64)	19 (4)	293 (60)
	NP/PA	11 (2)	0	11 (2)

RS, reagent strip; ANC, absolute neutrophil count; IQR, interquartile range; NP, nurse practitioner; PA, physician assistant.
[a] Data incomplete in 12 assessments.
[b] Gram stain and culture performed on 286/330 and 292/330 patients, respectively.
[c] Data incomplete in 150 assessments.

ANC in a busy ED setting, make a RS with the ability to rapidly rule out SBP at the bedside an attractive option. Under the best conditions, using a threshold of "trace" positive at 3 min, the Periscreen RS demonstrated a high sensitivity of 95%. However, the lower bound of the 95% CI was only 82%, making it unlikely that one could safely rule out SBP with a negative RS alone.

There was only one patient who had a "negative" RS reading who was ultimately diagnosed with SBP. The negative reading was confirmed by two separate providers. The patient had a history of cirrhosis, previous paracenteses, and presented with abdominal distention. Peritoneal fluid ANC was 11,001 cells/mm^3. The patient received IV antibiotics and remained afebrile with normal vitals throughout the hospital stay. The stay was complicated by continuing worsening of renal function such that hemodialysis was initiated. We cannot explain how this case with a high ANC had reported RS readings that were negative. In every other sample with ANC >2500 cells/mm^3, all RS readings were strongly positive ("large"). We cannot exclude the possibility that samples or study forms were confused.

The RS in our ED ascites patients performed with similar sensitivity to that in a multicenter study involving outpatient and inpatient populations [9]. Also, since ED ascites patients include those who present primarily for a therapeutic paracentesis and those who require diagnostic paracentesis to rule out SBP, it is not surprising that our 6% incidence of SBP was in-between the 2% and 11% SBP rate in outpatients and inpatients, respectively, in that study [9].

The wide confidence interval surrounding the sensitivity limits our ability to recommend the RS as a stand-alone test to rule out SBP. In previous studies we found that clinical suspicion alone is also insufficiently sensitive to exclude SBP. However, it seems likely that in a low clinical suspicion patient, a negative RS after a paracentesis might safely allow discharge without any further testing. This approach was not part of the current study and would be an interesting direction for future research. If verified, using the test characteristics we found, nearly half of the low suspicion patients could be safely discharged after RS testing alone.

4.1. Limitations

There are several important limitations to our study. First, the inclusion criterion was that the provider believed that fluid analysis was indicated to exclude SBP in that patient. Thus, it is possible that we missed SBP cases by excluding those in which the clinician felt that fluid analysis was not indicated. However, both study EDs were involved in two previous research studies which demonstrated that physician clinical suspicion, without fluid analysis, was inadequate in ruling out SBP, so standard practice at each of these facilities was peritoneal fluid laboratory analysis. In addition, chart review of 25 paracenteses demonstrated all had been sent for fluid analysis. Second, 58% of patients who received a paracentesis were not enrolled in the study. However, chart review of 25 non-enrolled patients demonstrated that only 2 patients (8%) had SBP, similar to the incidence of SBP in enrolled patients. Third, we did not reach our goal number of SBP patients, thus generating larger confidence intervals for our primary outcome. This was due to the lower incidence of SBP in this study compared to 2 prior studies in the same hospitals (6% vs 12%) [4,5]. It is unclear why this occurred. One possibility of increased SBP prophylaxis was found to be unlikely as we found no such prophylaxis during a 25-chart review. Fourth, this is a colorimetric analysis and the presence of blood or severe jaundice can discolor the peritoneal fluid, limiting the utility of the test. However, in our study, only 16 (2.5%) of the RS analyses had the colorimetric strip discolored such that a reading could not be made.

4.2. Conclusions

In summary, bedside use of the RS in ED ascites patients undergoing paracentesis demonstrated high sensitivity for SBP. However, given the wide confidence intervals, we cannot recommend it as a stand-alone test. We recommend further study with a larger number of SBP patients, potentially combining a negative RS result with low clinical suspicion to effectively rule out SBP without formal laboratory analysis.

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Author contributions

BC and GWH conceived the study. BC, GWH, and REW assisted in obtaining funding. BC, REW, GWH, RNW and SC participated in submission to the IRBs. All authors had input into the final study design and recruitment of study subjects. RR, DIB, SC, REW, and RNW participated in education on the research project and enrollment. BC, REW, DV, and LM assisted in compiling and analysis of data. GWH and BC did statistical analysis of the data. BC prepared the final manuscript. GWH, REW, SC, and RNW participated in manuscript revision. BC takes responsibility for the paper as a whole.

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