

Full Length Research Paper

# The usefulness of urine reagent strips and semi-quantitative procalcitonin (PCT-Q) tests in the diagnosis of meningitis

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Bacterial meningitis is a serious infection of the central nervous system. On the other hand, aseptic meningitis is a benign self-limited disease. Differentiating both diseases is of great importance. Earlier studies using urine reagent strips and procalcitonin (PCT) for diagnosis of meningitis had given a high sensitivity and specificity rates reaching 100%. The main aim of this study was to evaluate the usefulness of two bedside diagnostic tests in the diagnosis of meningitis. These were urine reagent strips and semi-quantitative procalcitonin (PCT-Q) test. One hundred patients with clinical and laboratory data suggesting of meningitis were included in this study. Complete biological and biochemical laboratory examination of cerebrospinal fluid (CSF), and serum inflammatory markers were done. According to this work, the 100 patients were classified into 64 patients with bacterial meningitis and 36 patients with aseptic meningitis. The CSF samples were tested using urine reagent strips for protein, glucose and leukocytes; as well as for PCT-Q test to detect its ability in differentiating bacterial from viral aseptic meningitis. Positive bacterial culture is the gold standard in the diagnosis of bacterial meningitis but it yielded a very low positivity rate (combined Gram stain and cultures were positive in only 4%). Although CSF protein concentration and leukocyte count and serum CRP were significantly higher in bacterial than aseptic meningitis, there was a wide area of overlapping results between the two groups. The number of reagent strip results coinciding with the laboratory results was 72%, 64% and 48% for leukocytes, protein and glucose respectively. Sensitivity rates were moderate and the degree of agreement between CSF strip and laboratory results were increased with higher grades for leukocytosis. PCT-Q had a good discriminating ability in differentiating bacterial from viral meningitis. With a cutoff value of 0.5 ng/dL, it was positive in 87% of patients with bacterial meningitis and negative in 91% of cases of viral aseptic meningitis. The use of reagent strips for the diagnosis of meningitis can be used only as a preliminary screening test till the laboratory results became available. PCT-Q test was more sensitive in differentiating bacterial from viral meningitis but it cannot be used alone for this diagnosis.

**Key words:** Procalcitonin, meningitis, bacterial, cerebrospinal fluid (CSF), viral.

## INTRODUCTION

Acute bacterial meningitis is a major cause of death and disability worldwide. It is an endemic disease in Egypt. *Streptococcus pneumoniae* was the leading cause of bacterial meningitis in Egypt (42%), followed by *Haemophilus influenzae* (20%), *Neisseria meningitidis*

(16%) and *Mycobacterium tuberculosis* (16%) (Afifi et al.,

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2009). Bacterial meningitis is a life-threatening neurological condition and needs prompt parental antibiotics, while viral meningitis is a benign condition

with a good outcome. However, this differentiation is not always easy (Meynaar et al., 2011).

Urine reagent strips have been used to test urine, ascetic fluid and pleural aspirate to evaluate infection in these biologic fluids. These reagent strips may be a valuable rapid bedside diagnostic test for CSF pleocytosis, glucose and protein till the laboratory results are available (Ray et al., 2007).

Procalcitonin is a prohormone of the hormone calcitonin. It is produced by several cell types and many organs in response to pro-inflammatory stimuli, in particular by bacterial products (Giunti et al., 2010). A significant elevation of plasma PCT is found during sepsis and in bacterial meningitis. PCT expression is only slightly induced, if at all, by viral infections, autoimmune, neoplastic diseases, and trauma of surgical intervention (Suberviola et al., 2012).

The high diagnostic accuracy of serum PCT level has been suggested for differentiating between acute bacterial and viral meningitis. The use of a bedside PCT rapid assay can be used to guide appropriate therapy for meningitis cases (Oh et al., 2009). So we aimed to assess the utility of two bedside diagnostic tests in the diagnosis of meningitis: urine reagent strips (combur-10) as well as the diagnostic accuracy of serum procalcitonin (PCT-Q) for differentiating bacterial from viral meningitis.

## PATIENTS AND METHODS

This prospective study was conducted at Shebin El-Kom Fever Hospital on 100 patients from the first of July 2010 to 30 June 2011. Neonates were excluded from the start as they referred to the pediatrician from the start.

During the study period, any patient with clinical picture suspecting the presence of meningitis was evaluated by the following: full history taking including fever, headache, vomiting, photophobia, and irritability. Also complete clinical examination was done to detect signs of meningeal irritation such as neck rigidity, Kernig and Brudzinski signs, altered conscious level, seizures, focal neurological signs, and skin rash. Full laboratory work up was done such as complete CSF analysis {culture, gram smears, cell counting and chemical tests (protein and glucose)}. Blood studies were tested in the form of white blood cells counting; total and differential, blood glucose, C-reactive protein and blood culture.

### Testing the CSF with rapid reagent strips

Combur-10 (Roche) reagent strip is a 10-patch test strip that is used to test urine for specific gravity, pH, leukocytes, nitrites, protein, glucose, ketones, urobilinogen, bilirubin, and blood. These test strips were

used in this study to measure CSF protein, glucose and leukocytes.

After 60 seconds (60 - 120 seconds for the leukocyte test area), the color change was red against the standards provided. The presence of leukocytes was graded as: negative, 1+ (10-25 cells/uL), 2+ (75 cells /uL), and 3+ (500 cells /uL) protein as: negative, 1+ (30 mg/dL), 2+ (100 mg/dL), and 3+ (500 mg/dL); and glucose as: normal, 1+ (50 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (1000 mg/dL) (Roche Combur-10, 2010).

### Meningitis patients grouping

According to the WHO bacterial meningitis case definition (Campagne et al., 1999), meningitis patients were classified into two groups:

1. Bacterial meningitis: Patients with a positive Gram stain and/or CSF culture or positive blood culture with concurrent meningitis; or detection in the CSF of >100 white blood cells per ml (number=64 cases).
2. Aseptic meningitis: CSF pleocytosis ( $\leq 100$  WBCs); negative Gram stain; and the CSF and blood cultures were negative for bacterial meningitis (number=36 cases) (Michos et al., 2007).

Bacterial meningitis cases were either confirmed (number = 27) with positive Gram stain and/or bacterial culture, or presumed bacterial meningitis (number = 37) with neutrophilic CSF and leukocyte count  $>4,000$  / mm<sup>3</sup> in the absence of bacterial isolate (Farag et al., 2005).

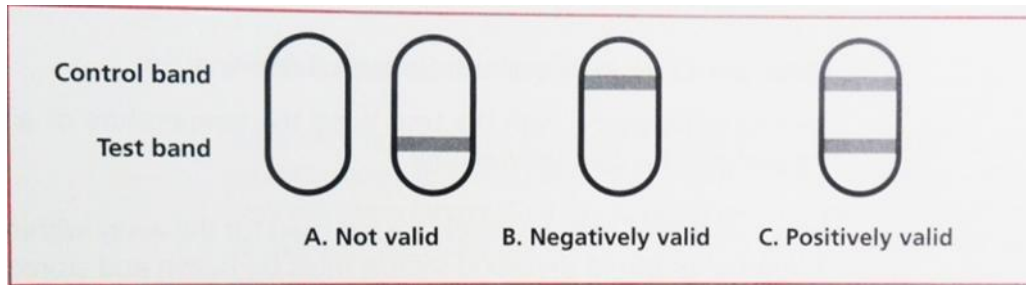
Presumed viral aseptic meningitis cases (number = 36) were cases with negative CSF Gram staining, negative CSF and blood cultures for bacterial infection, CSF protein level  $<80$  mg/dl, CSF pleocytosis ( $<100$ /mm<sup>3</sup>) with a predominance of mononuclear cells, blood neutrophil count  $< 10,000$ , negative CRP, no seizures, and recovery without antibiotic treatment (Dubos et al., 2010).

The PCT-Q (B.R.A.H.M.S Diagnostica, Germany) is an immune-chromatographic test for the semi-quantitative detection of PCT (pro-calcitonin). B.R.A.H.M.S PCT-Q is a test system with an incubation period of only 30 min, which neither depends on apparatus, nor needs calibration. The test uses a monoclonal mouse anti-catacalcin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase) (BRAHMS PCT-Q instruction manual, version R02us, 2007).

Results of PCT test in the two groups were compared with other laboratory results to characterize the ability of this bedside rapid test to differentiate bacterial from viral meningitis (Figure 1).

### Statistical analysis

Data were collected and statistically analyzed using



**Figure 1.** Checking the validity of the PCT test with the help of the clearly visible control band.

**Table 1.** Validity of CSF strip testing for leukocytes (in different grades) in comparison to CSF laboratory results (in different grades).

Strip Lab.	Sens. (%)	Spec. (%)	Acc. (%)	PPV (%)	NPV (%)
Grade-1 (10-25)	72	90	83	94	13
Grade-2 (25-75)	33	91	79	88	26
Grade-3 (75-500)	80	100	93	98	21.7

SPSS version 11 statistical package. Comparison of qualitative data was performed with chi square ( $\chi^2$ ) test. The validity of screening tests were measured and expressed as sensitivity, specificity, accuracy, positive predictive value, and negative predictive value (in comparison to diagnostic tests). The level of significance was considered at 5%. The highly significant level was at <0.01 or less.

Spearman correlation coefficient test was used for correlation of the non-parametric quantitative data between the two groups. Also, Mann-Whitney test was used for comparing the non-parametric quantitative data between the two groups.

## RESULTS

Between July 2010 and June 2011, a total number of 100 cases were admitted to Shebin El-Kom Fever Hospital with the clinical suspicion of meningitis for whom a lumbar puncture was performed to establish the diagnosis.

The demographic data of the studied patients showed no statistically significant difference among different age groups. Meningitis affected males more commonly than females, with a sex ratio of 1.5:1. This male preponderance was highly significant. Regarding the clinical manifestations, they were found to be of little assistance in differentiating bacterial from aseptic meningitis. There was a non-significant difference between patients with bacterial and aseptic meningitis regarding most of the clinical data. The only exceptions were Kernig sign, Brudzinski sign, altered consciousness level and localizing neurological signs which were found to be significantly higher in bacterial than aseptic

meningitis.

The frequency of the identified organisms causing meningitis was calculated by microscopy and/or culture. Among the 27 patients where the causative organism was identified, *S. pneumoniae* was the most frequently isolated (51%). *N. meningitidis* was the second (22%). *H. influenzae* occurred in 14%, while *M. tuberculosis* was responsible for 13% of cases. A significant difference between both groups was found for both leukocyte count and CRP.

### Usefulness of two bed-side diagnostic tests

#### *Use of urine reagent strips in the diagnosis of meningitis*

The relation between the reagent strips and laboratory values for CSF leukocyte count, protein and glucose revealed that the number of laboratory values that fell within the range set by cut points was 64% for glucose, 51% for protein, and 71% for leukocytes.

On comparing the negative results (grade 0) of CSF strip testing for leukocytes, Ptn and glucose with CSF laboratory results, it appeared that they matched each other as the samples were negative. For other grades, the degree of agreement between the two results was increased with higher grades as presented in Table 1.

#### *Serum PCT in differentiating bacterial from viral meningitis*

From the results of PCT-Q testing in bacterial and viral meningitis groups, it was found that PCT testing was negative (that is, PCT <0.5 ng/mL) in 33 cases (91.6%)

**Table 2.** Comparison between bacterial and viral meningitis studied groups regarding procalcitonin level.

Procalcitonin level	Bacterial meningitis		Viral meningitis		Total		P
	No.	%	No.	%	No.	%	
<0.5	8	12.5	33	91.6	41	41	P<0.0001
≥0.5	6	9.4	2	5.6	8	8	
>2	17	26.6	1	2.8	18	18	
>10	33	51.5	0	0	33	33	
Total	64	100	36	100	100	100	

p<0.001: highly significant.

**Table 3.** The sensitivity, specificity, accuracy, positive and negative predictive values of serum PCT for bacterial meningitis patients.

Variable	PCT values		Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %
	+ve ≥0.5 ng/ml	-ve <0.5 ng/ml					
Bacterial meningitis	56	8	88	92	89	95	80
Non-bact. meningitis	3	33					

with viral meningitis, and only 8 patients (12.5%) had bacterial meningitis. PCT-Q testing was positive (≥0.5 ng/mL) in 56 patients (87.5%) with bacterial meningitis, and in only 3 cases (8.4%) with viral meningitis as illustrated in Table 2.

Procalcitonin level among cases of meningitis was significantly higher in cases with vomiting, irritability, positive neck rigidity and those with altered consciousness than negative cases regarding the previous manifestations (p<0.01, 0.05, 0.01 and 0.0001 respectively). On the other hand, the level of procalcitonin was significantly higher among cases with bad outcome (death), than those with good outcome (p<0.01).

Table 3 shows the sensitivity, specificity, accuracy, and positive and negative predictive values of serum PCT for bacterial meningitis patients. Serum PCT with cutoff value of ≥0.5 ng/mL showed a high accuracy rate (89%) for the diagnosis of bacterial meningitis with a good sensitivity and specificity rates.

There was a positive correlation between CRP blood level and procalcitonin level (p<0.0001) (Figure 2). Regarding CSF analysis in meningitis cases, there was a positive correlation between protein level and procalcitonin level (p<0.0001) (Figure 3). CSF neutrophilic count also offered a high positive significant correlation with the procalcitonin level (p<0.0001) (Figure 4) while procalcitonin level exhibited a negative correlation with the CSF glucose level.

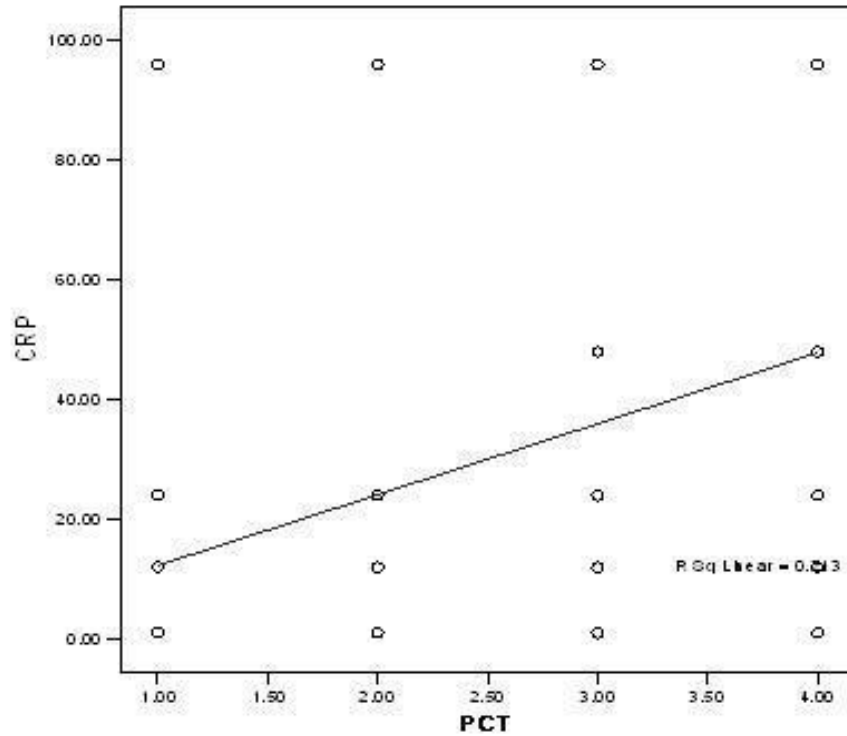
## DISCUSSION

Meningitis cases were distributed equally in all age

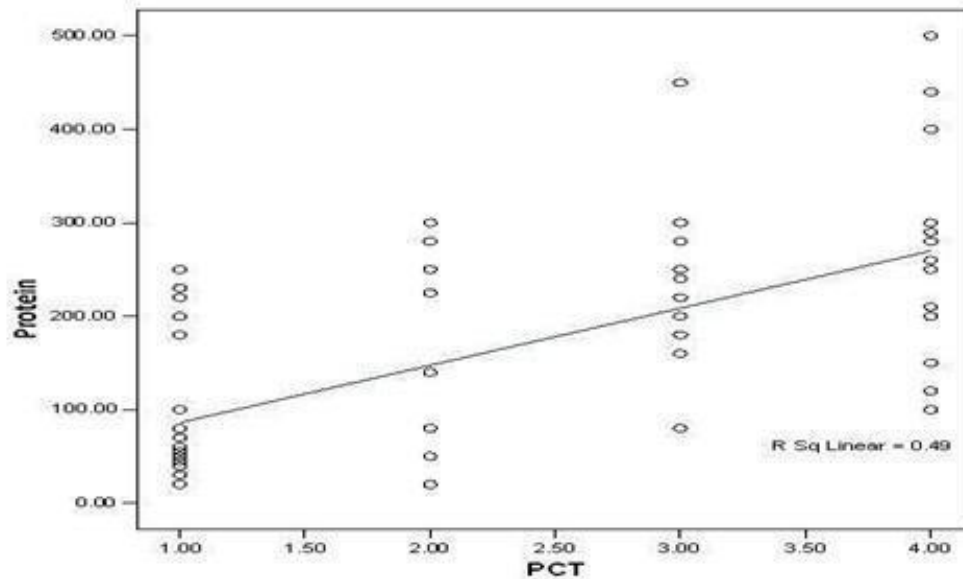
groups. The availability of effective vaccines against common pathogens causing meningitis may have resulted in a somewhat shift of age incidence towards adulthood as vaccination started at the age of 2 years up to 55 years (Centers for Disease Control and Prevention CDC, January 2011). In the United States, bacterial meningitis is now a disease predominantly of adults rather than of infants and children as a result of implementation of *H. influenzae* vaccine in 1990 (Dery and Hasbun, 2007). In the current study, meningitis cases were distributed equally in all age groups as effective vaccine against common pathogens causing meningitis but are not widely distributed in Egypt until now.

This study's data showed that in patients with meningitis, the triad of meningeal inflammation, that is, fevers, headache and neck rigidity was found in 87, 80 and 69% respectively. Similar rates were reported by several investigators in Egypt. Afifi et al. (2007) in their study found that 78% of patients had neck stiffness, and 60% presented with headache. Signs of meningeal irritation were found to be more frequent in patients with bacterial meningitis and this went hand in hand with the study that was done by Estal et al. (2010), who reported results close to our results.

At the time of presentation to the hospital, 40% of our patients had an altered state of consciousness (ranging from lethargy to coma), 23% presented with seizures and 5% of patients had localizing neurologic signs (for example, cranial nerve paralysis, aphasia, or hemiparalysis). These neurologic manifestations are related to the severity of the disease and the time interval before



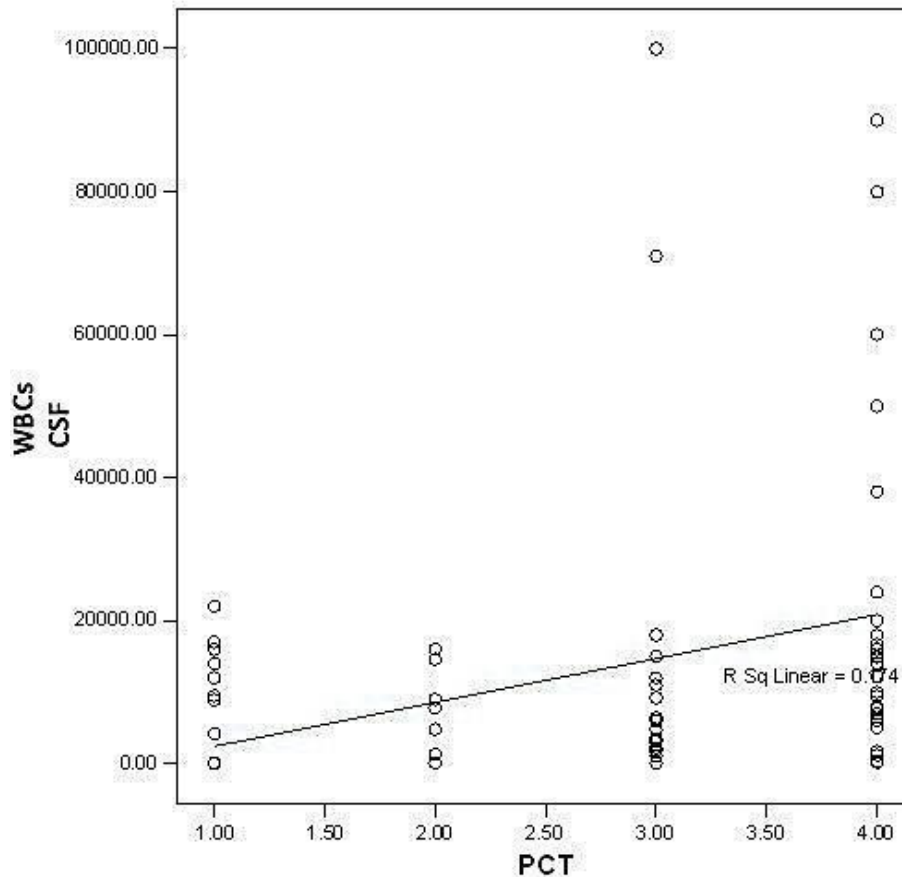
**Figure 2.** Correlation coefficient of PCT levels with CRP level.



**Figure 3.** Correlation coefficient of serum PCT with CSF protein level.

arrival to the hospital. In one study, altered consciousness level and seizures were present in 9% and 19% respectively (Amarilyo et al., 2011). The rate of seizures among patients with acute bacterial meningitis has been reported to be from 12 to 27% (Kimia et al., 2010).

Skin rash (of any type) was recorded in only 3% of our cases. In the study of Afifi et al. (2007), skin rash was reported in 2 to 16% according to causative organism. Also, Arda et al. (2008) reported an incidence rate of 9.3% for skin rash in adult patients with acute purulent meningitis.



**Figure 4.** Correlation coefficient of PCT levels with CSF leukocyte count level.

Our meningitis patients were divided into two groups: bacterial and aseptic (64 and 36 patients) respectively. Bacterial meningitis group included both confirmed cases in which an etiologic pathogen was identified by either bacterial culture and/or Gram stain; and suspected bacterial meningitis with a CSF leukocyte count  $>100$  cell/mm<sup>3</sup>. The second group, that is, aseptic meningitis is defined as meningitis in which no bacterial pathogen can be isolated by routine cultures, and a clear CSF with a leukocyte count  $\leq 100$  cell/mm<sup>3</sup>. This stratification of meningitis patients was based on the WHO case definition of bacterial meningitis (Nigrovic et al., 2009; Mwaniki et al., 2011).

The ratio of bacterial to aseptic meningitis cases differed between different studies. In one study, 48.5% of meningitis patients had bacterial meningitis (Dubos et al., 2008). However, in the study of Amarilyo et al. (2011), bacterial meningitis was diagnosed in 10.3% of meningitis patients and 89.7% of cases were aseptic. This difference in the percentage of bacterial versus aseptic meningitis can be attributed to differences in the place and time of studies done, so, in developing countries bacterial meningitis was the major constituent of meningitis cases, while in developed countries and especially after the

implementation of anti-capsular vaccines, bacterial meningitis became a rare event in relation to viral meningitis.

The classic clinical presentation of bacterial meningitis includes stiff neck, headache, fever, photophobia, malaise, vomiting, irritability, and lethargy. There is a progressive deterioration in the level of consciousness from lethargy to stupor and then obtundation and coma (Pfister and Roos, 2003). Aseptic meningitis syndrome is associated with symptoms, signs, and laboratory evidence of meningeal inflammation. Clinically, patients usually appear non-toxic but may have changes in mental status, including irritability. Other signs of viral infection may include pharyngitis, adenopathy, morbilliform rash, and myalgia. There are usually no signs of vascular instability (Rotbart, 2000). On comparing both groups of bacterial and aseptic meningitis in our study regarding their clinical manifestations, only altered consciousness level, localizing neurologic signs and Kernig sign were found to be highly significant in bacterial than aseptic meningitis.

CRP is the classic acute phase reactant, and CRP levels in serum and CSF have been shown to be increased as a result of invasive CNS infection (Dubos et

al., 2008). In our work, CRP levels more than or equal to 6 mg/dL in serum were considered positive and were taken as a cut-off value to differentiate bacterial from aseptic meningitis. CRP results were positive in 74% (mean value of  $27 \pm 28.1$ ) of patients with bacterial meningitis, and 15% (mean value of  $4.2 \pm 0.1$ ) of patients with aseptic meningitis. The same significant difference for CRP between bacterial and non-bacterial meningitis was reported by Alkholi et al. (2011).

As regards the urine reagent strips, we found that the number of reagent strips results coinciding with the laboratory results (values that fell within the range set by the cut-off points previously determined), that is, the concordance rate between the laboratory assay and reagent strips results was 72% for leukocytes, 64% for protein, and 49% for glucose. A higher rate of agreement between reagent strips and laboratory results was reported by Parmar et al. (2004); in their work, the number of laboratory values that fell within the range set by the cut-off points was 87.2% for glucose, 88.5% for protein, and 96.6% for leukocytes. Moosa et al. (1995) found a good agreement between reagent strips and laboratory results for the diagnosis of meningitis, with a sensitivity of 97% and specificity of 100%.

This study agrees with that of Koulaouzidis (2011) that caution is needed in the use of reagent strips for the diagnosis of meningitis, because this test is subjective, especially in cases with slightly altered CSF; therefore the method is considered qualitative or semi-quantitative. Interest in markers that can differentiate bacterial from viral meningitis has been growing (Dellinger et al., 2004). An ideal marker for bacterial infections should allow early diagnosis, inform about the course and prognosis of the disease, and facilitate therapeutic decisions. PCT was said to cover these features best as compared to other commonly used biomarkers. A superior diagnostic accuracy of PCT has been shown for a variety of infections, for example, respiratory tract infections, acute infectious endocarditis, shock, and pancreatitis (Crain and Müller, 2005).

PCT is an early marker of bacteraemia, as such several authors have reported the quantitative evaluation of PCT as a diagnostic marker of bacteremia quoting sensitivity and specificity ranging from 57 to 100% (Franz et al., 1999). PCT-Q can be a useful tool in emergency departments since the fast diagnosis can help in initial therapeutic decision making (results available in 30 min); it is also useful in hospitals not equipped with a measuring device to determine PCT concentrations (non-instrument based test) (Prat et al., 2004).

In this study, we used the rapid semi-quantitative PCT-Q bedside diagnostic kits for determination of serum PCT level in patients with either bacterial or viral meningitis with the aim of determining its accuracy to differentiate between those two groups of meningitis. We used a cut-off PCT level  $>0.5\text{ug/dL}$  to distinguish patients with bacterial meningitis from those with viral meningitis (56

patients with bacterial meningitis out of 64 had a serum PCT level  $>0.5\text{ug/dL}$  and 33 out of 36 patients with viral meningitis had a serum PCT level below this level) with a sensitivity of 87.5% and a specificity of 91%. With a higher PCT serum levels, that is,  $>2\text{ug/dL}$ , the specificity of serum PCT increased to 97.3% but the sensitivity decreased to 78%. Several studies confirmed that a high serum PCT level is the best biological predictor for distinguishing between bacterial and aseptic meningitis. Dubos et al. (2008) found that a PCT used alone at a  $0.5\text{ug/dL}$  offered the best sensitivity (99%) and specificity (83%). Similarly, Dubos et al. (2006) found that a PCT  $\geq 0.5\text{ug/dL}$  and a CSF protein  $\geq 0.5\text{g/L}$  were the best biologic tests with 89 and 86% sensitivity rates, 89 and 78% specificity rates.

This study showed that the level of PCT was significantly higher among patients with severe manifestations of meningitis, for example, neck rigidity, and altered consciousness, and also, among cases with bad outcome. Also, there was a highly positive correlation between serum CRP level, CSF protein levels and PCT level. Such correlation was reported in a study by Bishara et al. (2007).

In our work, PCT is a more reliable marker of bacterial meningitis versus other parameters. It is a quick diagnostic test (available in 30 min), non-instrument based. PCT has a prognostic value as it is significantly higher in non-survivors during this study versus survivors. Although PCT is not a substitute for careful history taking and physical examination, a clinician should withstand the temptation to rely solely on the result of a laboratory test rather than to interpret a demanding clinical examination. As is the case for all diagnostic tests, a serum PCT level must always be evaluated and re-evaluated.

## Conclusion

We can conclude that no single test can be used alone with 100% sensitivity for diagnosing meningitis and for differentiating bacterial from viral meningitis. Caution is needed in the use of reagent strips for the diagnosis of meningitis. They can be used only as a preliminary screening test. PCT-Q had a higher sensitivity in differentiating bacterial from viral meningitis than other inflammatory biomarkers. However, it can not be used alone for this diagnosis.

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