

## Evaluation of Procalcitonin Test for Early Diagnosis of Neonatal Sepsis in Tikrit Teaching Hospital



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### ABSTRACT

The diagnosis of neonatal infection is challenging because traditional markers of infection are often misleading instead of diagnosing. This study was conducted to determine Procalcitonin (PCT) level as an early marker for diagnosis of suspected sepsis in neonates in comparison with C-reactive protein, blood culture, total and differential white blood cell counts. From August, 2008 till March, 2009, 114 blood samples were collected from neonates (males and females) admitted to the pediatrics-neonatal wards at Tikrit Teaching Hospital who were clinically suspected with sepsis as diagnosed by the physician in the hospital with any features suggestive of sepsis. The results of blood culture showed that 53 (46%) of samples were positive, of them 32 (60%) were males and 21 (40%) were females. The number of negative cases were 61 (54%), of them 31 (51%) were females and 30 (49%) were males. The results of identification showed that the most frequent bacterial isolates were Coagulase Negative Staphylococci and *Nocardia* spp. (22% for each), followed by *Listeria monocytogenes* 17%, *Klebsiella pneumoniae*, 9% *Pseudomonas aeruginosa* 6% and *Staphylococcus aureus* 6%, while (*Citrobacter diversus*, *Serratia marscesens*, *Serratia liquifascens*, *Lactobacillus* spp., *Peptostreptococcus* spp., *Micrococcus* spp., *Streptococcus pyogenes*) were frequently less isolated recording 2% for each .

The antibiotics susceptibility test revealed that Gram negative isolates showed high resistance to antibiotics used in the present study. Each isolate of the Gram positive bacteria showed different pattern of resistance against the antibiotics used. Results of virulence factor showed that 85%, 100%, 100% , 100% and 62% of Gram negative isolates and 61%, 100% , 89%, 94% and 78% of Gram positive isolated produced Urease , Hemolysin, Lipase, Lecithinase and alkaline protease, respectively. Results of routine hematological tests at which the differences were statistically significant showed that 33% of culture positive cases had leucopenia, 19% of cases had leukocytosis, while the rest were in the category of normal range. For CRP, the differences were not significant among culture positive and culture negative cases. With reference to PCT test which had been measured using the immunochromatographic semi-quantitative method. The results showed that 21% of culture positive cases were with PCT level <0.5 ng/ml (which were regarded as negative), while the rest which were with high levels distributed among levels of  $PCT \geq 0.5 \geq 2 \geq 10$  ng/ml. As for culture negative cases, 49% of PCT were <0.5 ng/ml, while 51% of cases were in levels of  $\geq 0.5 \geq 2 \geq 10$  ng/ml which means that systemic infections cannot be excluded though they were culture negative. In addition PCT results did not fit with CRP all the time since some cases recorded higher level of  $PCT \geq 10$  ng/ml despite they were negative for CRP. The comparison between results of PCT and WBC for the same performed cases showed that 68% of cases were in the category of normal WBC range, meanwhile they had high level of PCT. Only 18% were in the category of leukocytosis, and the rest of percentage were in the category of leucopenia. When PCT was compared with other routinely measured parameters used in this study, It seemed to be significantly more sensitive in sepsis diagnosis. Accordingly, we can conclude that PCT is a more sensitive marker than other traditional tests (blood culture, CRP and WBC count) that could be used in early diagnosis of bacterial sepsis in neonates.

## Introduction

In modern usage, sepsis is defined as the growth of microorganisms in blood and other tissues (1). It is a clinical condition in which an infectious illness results in systemic toxicity and can ultimately result in irreversible shock. It is virtually always caused by a blood-borne bacterial illness. Bacterial sepsis is far more common in neonates and young infants than in healthy older children or adults (2,3,4). "sepsis" has alternately been called septicemia (5). Neonatal sepsis can be a generalized infection such as septicemia or may be a localized deep-seated infection such as pneumonia or meningitis (6).

Neonatal sepsis presents during three periods. Early-onset sepsis often begins in utero and usually is due to infection by bacteria of the mother's genitourinary tract. These organisms include group B streptococcus, *E. coli*, *Klebsiella* spp., *Listeria monocytogenes* and nontypable *Haemophilus influenzae* (7).

Late-onset neonatal infection (8-28 days of life) usually occurs in the healthy full-term infants who were discharged in good health from the normal newborn nursery. Late-onset sepsis may be caused by the same pathogens as early-onset sepsis, but those infants exhibiting sepsis late in the neonatal period may also have infections caused by pathogens usually found in older infants (7,8).

Nosocomially acquired sepsis (8 day to discharge) occurs predominantly among premature infants in the Neonatal Intensive Care Units (NICU); many of these infants have been colonized with the multidrug-resistant bacteria indigenous to the NICU (7).

Clinical manifestations are often vague and nonspecific. Alteration in feeding pattern such as refusal to feed is the most characteristic early feature. Lethargy, poor activity, hypothermia, fever (temperature instability), vomiting, abdominal distension, tachypnea, chest retractions, apnea, seizures, cyanosis, jaundice, pallor, shock, sclerema are clinical features of the disease (6).

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Early recognition, diagnosis and treatment of serious infection in the neonate is essential because of the risk of permanent morbidity or mortality (9,10). Progression from mild symptoms to death can occur in less than 24 hours. Most neonatal bacterial infections have an early bacteraemic phase preceding the development of a full-blown septicaemia or the localization of infection in organs and tissues (10). Because the initial clinical manifestations often are non-specific, the early clinical diagnosis of neonatal sepsis is difficult. The decision to perform a partial or extended evaluation and to institute antimicrobial therapy remains a matter of clinical judgment. The diagnosis of neonatal infection is challenging because traditional markers of infection are often misleading (11). The present study is the first study in Iraq to evaluate the Procalcitonin as a sensitive marker for early diagnosis of neonatal sepsis in comparison with other commonly used diagnostic methods.

## Materials and methods

### Sample Collection

From August, 2008 till March, 2009, samples were taken from neonates (males and females) admitted to the pediatrics-neonatal wards at Tikrit Teaching Hospital who were clinically suspected with sepsis as diagnosed by the physician in the hospital with any features suggestive of sepsis. Neonates who received antibiotics were excluded from the study. The study includes a total of 114 cases (peripheral blood samples were obtained from 114 samples). Blood culture was taken from all cases. While the other tests (total and differential WBC count, CRP, PCT) were not performed for all cases due to the inadequate amount of blood. The blood was immediately added to a sufficient volume of (BHI) broth 1: 10 and were thoroughly mixed to prevent clotting, therefore no anticoagulant was needed (12). The second ml was put in a tube containing EDTA (surly after removing the needle of the syringe). The rest of blood sample was transferred to a plain tube to gain the serum. A serum sample was frozen for later determination of the Procalcitonin level and for C-reactive protein (13).

### Hematological tests (WBCs count)

#### -Total WBCs count procedure

The total WBCs count was performed according to (14, 15).

#### - Differential WBCs count

Blood films were done on glass slides. Romanowsky stains were employed for blood films staining. The films stained as soon as they had dried in the air, and

certainly they were not left unfixed for more than a few hours (15,16). The film was examined with an oil immersion objective. Each leukocyte seen was classified and the percentage of each cell type was calculated with recording tabulator. Leukocytes were counted in different part of the film (14).

#### - Blood culture

Blood – culture bottles were incubated at 35-37°C and were routinely inspected.

For the first sight, growth was evidenced by:

A floccular deposit on top of the blood layer

- Uniform or substrate turbidity
- Coagulation of the broth
- A surface pellicle
- Production of gas
- White grains on the surface or deep in the blood layer
- Some microorganisms grew without producing turbidity or visible alteration of the broth. Others tend to undergo autolysis and die very rapidly. Subcultures were performed on appropriate media (12).

#### - Identification of bacterial isolates

Initial identification started with performing a Gram stain (manufactured by : ARCOMEX Jordan), observing colony morphology, and assessing the organism's ability to ferment glucose and grow on MacConkey agar. Pigment production of isolates was also noticed (17). The identification was completed using biochemical tests such as Catalase test, Oxidase test, Indole test, Methyl Red Test, Voges-Proskauer Test, Citrate Utilization Test (18,19), Urease test, Deoxyribonuclease (DNase) test (20), Coagulase test (21), Hallotolerance test (22).

#### -Antibiotic sensitivity test

All isolated bacteria were tested for antibiotic sensitivity according to (23).

#### - Qualitative detection of some virulence factors

The isolated bacteria were tested for their ability to produce Urease, Lecithinase- Lipase production according to Balows *et al.*, (1991) (24) and from the production of Hemolysin and Protease (Casein Hydrolysis test) according to Lennette *et al.*, (1985) (25).

#### - Determination of C-Reactive Protein (CRP) level in serum

The assay was performed by testing a suspension of latex particles coated with anti-human CRP antibodies against unknown serum. The presence of visible

agglutination indicates an increase in level of CRP to a clinically significant level (26). The CRP Latex test kit was manufactured by the British company Plasma tec /plasmatic laboratory product ltd.

#### -Immuno chromatographic test for the determination of procalcitonin in serum

##### - Contents of the kit :

**This kit is for *in vitro* use only** It contains the following components in sufficient quantities for 25 individual determinations

- 25 individual test sets
- 25 reference cards
- 1 user leaflet

Each individual test set is sealed in a protective packaging and

contains

- 1 individual test
- 1 disposable plastic pipette
- 1 dry bag

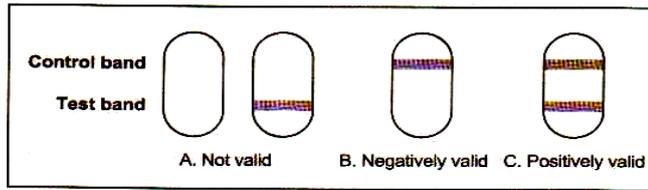
##### - Principles

The B·R·A·H·M·S PCT@-Q is an immuno chromatographic test for the **semi-quantitative detection of PCT** (procalcitonin), which is used for diagnosing and controlling the treatment of severe bacterial infection and sepsis. B·R·A·H·M·S PCT@-Q is a test system with an incubation period of only 30 minutes, which neither depends on apparatus, nor needs calibrating. The test uses a monoclonal mouse anti-catacalcin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anticalcitonin antibody (solid phase). After the patient sample (serum or plasma) has been applied to the test strip, the tracer binds to the PCT in the sample and a marked antigen antibody complex forms. This complex moves by means of capillarity through the test system and, in the process, passes through the area containing the test band. Here, the marked antigen antibody complex binds to the fixed anticalcitonin antibodies and forms a sandwich complex.

At a PCT concentration  $\geq 0.5$  ng/ml, this sandwich complex can be seen as a reddish band. The colour intensity of the band is directly proportional to the PCT concentration of the sample and is related to the following **PCT concentration ranges** with the help of a reference card:

**$< 0.5$  ng/ml  $\geq 0.5$  ng/ml  $\geq 2$  ng/ml  $\geq 10$  ng/ml**

Non-bound tracer diffuses into the control band zone, where it is fixed and produces an intensely coloured red control band. The functional ability of the test system is checked by means of this control band as shown in the below figure (13).



#### - Test procedure

- 1) **200 µl of serum/plasma was dripped by a micropipette** into the round cavity. Or, **6 drops** Dripped by the enclosed dropper pipette into the round cavity of the B·R·A·H·M·S PCT -Q. The pipette was filled to at least the measuring line without any bubbles ,and held slightly tilted when used (temperature of all components was brought to room temperature).
- 2) Incubation for 30 minutes at room temperature. the time was documented on the reference card when the test was begun.
- 3) **Recording and assessment / after 30 minutes** (max. 45 minutes), the PCT concentration range of the sample was determined. Firstly, the validity of the test was checked with the help of the clearly visible **control band** .
- 4) **Documentation and archiving** the test result, the concentration range , which corresponds to the color intensity of the test band, were documented by a cross mark on the reference card <sup>(27)</sup> .

#### -Statistical Analysis

Statistical analysis were performed using the Chi-square, t- test and Analysis of Variance (ANOVA) test (the means of treatments were compared by Duncun's Multiple Range test), under the level of significancy ( $p \leq 0/05$ ) <sup>(28)</sup> .

#### Results and Discussion

A total of 114 neonates admitted to the pediatric and neonatal units at Tikrit Teaching Hospital from August, 2008 till March, 2009 with clinically diagnosed or suspected sepsis were enrolled in this study. Both males and females were included, of them 62 (55%) were males while 52 (45%). Blood cultures were done for all cases. Hematological tests ( including total and differential white blood cells count ) were performed for 102 cases. C- reactive protein was determined in 84 cases, while Procalcitonin level was determined in 73 cases. The differences in the number of samples involved in each test were due to the inadequate amount of blood specimens to perform all investigations especially for those neonates with low or very low or extremely low birth weight.

Figure (1) shows results of blood culture, 53 (46%) of samples were culture positive, 32 (60%) were males and 21 (40%) were females. The number of negative cases were 61 (54%), of whom 31 (51%) were females and 30 (49%) were males. The culture positive rate in a study conducted by Al- Bayaa, (2005) was 30.4%, she elucidated that due to the antibiotic abuse and/or the small amount of the withdrawn blood samples <sup>(29)</sup> .

The isolated bacteria were identified according to microscopical, macroscopical and biochemical test. *Peptostreptococcus spp.* was identified in one cases using anaerobic gas-Pac system for incubation .

The results of identification showed that the most frequent bacterial isolates were *Nocardia spp.* and Coagulase negative staphylococci (22% for each) , Followed by *L. monocytogenes* 17%, *K. pneumoniae* 9% *P. aeruginosa* 6% and *Staphylococcus aureus* 6%, while (*C. diversus* , *S. marscesens*, *S. liquifascens*, *Lactobacillus spp.*, *Peptostreptococcus spp.*, *Micrococcus spp.*, *Streptococcus pyogenes*) were frequently less isolated, recorded 2% for each (table 1) .

Figure (2) below reveals that Gram positive bacteria was predominant 75% in comparison with Gram negative bacteria 25% , which correlated well with the findings of Fuchs and Sanyal, (2008) who found that gram-positive organisms have been increasingly identified as the source of sepsis and currently surpass gram-negative pathogens as the etiologic agents of sepsis <sup>(30)</sup> .

In a recent review of bacteremic *Nocardia* infections, *N. asteroides* was found to be the predominant pathogen, while bacteremic disease due to *Nocardia nova*, *Nocardia otitidiscaviarum*, and *Nocardia farcinica* was less commonly encountered <sup>(31)</sup> .

Fifty one isolates were examined for their susceptibility to antibiotics using agar dilution method according to NCCLS guidelines. The results showed that most Gram negative isolates were resistant to most tested antibiotics since , all isolates were resistant to erythromycin, rifampicin, vancomycin, ampicilin, cefotaxime and tetracycline (table 2) . This resistance may be due to the fact that some antibiotics can not penetrate the outer membrane which might decrease the permeability for the drug .

As for Gram positive bacterial isolates , each isolate of the Gram positive bacteria showed different pattern of resistance against the antibiotics used (table 3) .

The high resistance pattern for antibiotics might be due to the mechanisms of resistance which involve the alteration of the target to which antimicrobial agents bind . or alteration in membrane permeability , enzymes and metabolic pathways which are usually caused by the acquisition of R plasmids <sup>(32)</sup> . In addition The relatively nonspecific efflux pumps that can pump many different drugs could explain the resistance of these isolates <sup>(33)</sup> .

Among the total Gram negative isolated bacteria (13 isolates), eleven 85% were able to produce Urease enzyme ,while among the Gram positive bacteria ( 36 isolates ), 20 (61%) isolates produced this enzyme, while the rest were negative as shown in figure(3 - picture 1) and tables ( 4 and 5) .

According haemolysin ( $\beta$  type) the results of the current study revealed that all isolates had the ability to produce this factor (tables 4 and 5) , which agreed with Furumura *at al.*, (2006) who stated that hemolysin is commonly produced by Gram-positive and Gram negative bacteria and, in most cases, is considered to be a virulence factor, although its relative contribution to disease is variable among microbes and different host species <sup>(34)</sup> .

The results showed that among Gram negative bacteria all isolates (100%) were positive for lipase production disagreed with Ali, (2007) who stated that *E. coli*, *K. pneumoniae* and *Citrobacter* didn't produce lipase <sup>(35)</sup> . Among Gram positive bacteria Thirty two (89%) were positive for lipase production. All isolates of *Nocardia spp.* were positive , same thing with *Staph. aureus*, *L. monocytogenes* and *Lactobacillus spp.*, while nine isolates of Coagulase negative staphylococci were positive . GAS was negative for lipase production (tables 4 and 5).

Lipase acts on triglycerides , cleaves bond between glycerol and fatty acids <sup>(36)</sup> . Figure (3 – picture 2) reveals production of lipase.

The results showed that among Gram negative bacteria all isolates were positive for lecithinase production. Among Gram positive bacteria thirty four (94%) were positive for lecithinase production. All isolates of *Nocardia spp.* Were positive, same thing with *Staph. aureus*, *L. monocytogenes* and *Lactobacillus spp.*, while eleven isolates of Coagulase negative staphylococci was positive . GAS was negative for lecithinase production ( tables 4 and 5).

Lecithinase destroys red blood cells and other tissue cells, It is active in phosphatidylserine and phosphatidylcholine PC degradation. Lecithinase

hydrolyzes lecithin which is a lipid component of eukaryotic membrane thereby this enzyme destroys the integrity of the cytoplasmic membranes of many cells. The two enzymes (lecithinase and Hemolysin) have a synergistic effect on the ability of the organism to invade host tissues <sup>(37,38)</sup> . Production of lecithinase is illustrated in Figure (3- picture 3)

The results showed that among Gram negative bacteria eight isolates were positive for protease production (62%) . Isolates of *C. diversus* , *S. marscecens* and *S. liquifascens* were negative for protease production , while three isolates of *K. pneumoniae* were positive . All *P. aeruginosa* isolates were positive ( table 4).

Among Gram positive bacteria, twenty eight (78%) were positive for protease production. Ten isolates of *Nocardia spp.* were positive . All isolates of *Staph. aureus* were protease positive. Eight isolates of both Coagulase negative staphylococci and *L. monocytogenes* were positive, *Lactobacillus spp.* produced protease , while GAS did not (table 5) . Hamadah (2008 ) who worked only on *Staph. aureus* stated that 58% of his isolates produced protease <sup>(39)</sup> .

Alkaline protease cleaves laminin associated with basement membranes <sup>(33)</sup> . It degrades a variety of host proteins and have a direct destructive effect on skin tissue <sup>(40)</sup> . Production of protease is shown in figure (3- picture 4).The isolates that produced alkaline protease were further distributed according to the diameter of clear zone a round the wells as shown in tables 6 and 7.

Hematological tests were performed for 102 cases , of them 52 ( 51%) were culture positive and 50 (49%) cases were culture negative.

Table (8) shows distribution of total WBC count according to culture results. The differences were statistically significant since ( $p \leq 0.05$ ). The results showed that 33% of culture positive cases had leucopenia (decreased in numbers of WBC), 19% of cases had leukocytosis ( elevation of WBC) while the rest were in the category of normal range. Our results are in agreement with Gomella *et al.*, (2004) who reported that a normal WBC does not rule out sepsis and Only half of infants with WBC < 5000 or WBC > 20,000 have positive blood cultures <sup>(41)</sup> .

Table (9) shows distribution of ANC count in relation with culture results. Results of our study revealed that 19% of the culture positive cases had neutrophilia, 21% had neutropenia while the rest were in the category of normal range . As for culture negative

cases, results showed that large proportion (70%) were in the category of normal range and, only 12% of cases had neutrophilia and 18% had neutropenia. However, the differences between groups were statistically non significant.

This results is in agreement with Rennie, (2005) who stated that both neutropenia and neutrophilia have useful predictive power, although in neither case is the specificity or sensitivity greater than about 80%<sup>(10)</sup>, but disagreed with Bain, (2004) who reported that most patients with bacterial infection have a neutrophilia because large proportion of normal range neutrophil count were positive for culture and other investigations<sup>(16)</sup>.

CRP was performed for 84 cases. Table (10) shows distribution of CRP results according to culture, the differences were not statistically significant. Among culture positive cases 44% of cases were recorded as positive while the rest recorded negative for CRP. Concerning with culture negative cases, 29% were recorded as positive and, 71% were recorded as negative, agreed with Burner *et al.*, (1997) who stated that CRP did not elevated the whole time in proven septic cases<sup>(42)</sup>.

Cytokines stimulate hepatocytes to increase the synthesis and release of CRP<sup>(43)</sup>. CRP secretion starts within 4–6 hrs after stimulation, peaking only after 36 hrs<sup>(44)</sup>, this might give a clue why 56% of culture positive cases were negative for CRP. Procalcitonin is a well-established biomarker for the diagnosis of sepsis<sup>(45)</sup>. Alongside other calcitonin precursor peptides, PCT is found in the serum in physiological conditions, but the PCT levels detected are very low (<0.1 ng/ml). However, in septic patients, the PCT level increases, sometimes to the levels of more than several hundreds of nanograms per milliliter. The exact site of its production during sepsis is uncertain, although it is thought to be extrathyroidal<sup>(46)</sup>.

PCT was measured using the immunochromatographic (strip test) semi- quantitative method (B.R.A.H.M.S-PCT-Q) with different cut offs in ng/ml (<0.5; 0.5-2; 2-5; 5-10; > 10)<sup>(47)</sup>.

In the current study all serum-samples of neonates aged less than 28 hours were excluded, because PCT values are physiologically increased during the first two days of life. However PCT values of newborns suffering from early sepsis are significantly higher than those of healthy newborns<sup>(48)</sup>.

Seventy three cases were performed for PCT, of them 38 cases were culture positive and 35 cases were culture negative. Results of our study showed that 21% of culture positive cases were in the level <0.5ng/ml (clinically insignificant PCT response) which means minor or no significant inflammatory response and local infection is possible<sup>(49,50)</sup>. As for culture negative cases 49% of PCT were in the level of <0.5 ng/ml, while 51% from cases were in the levels of  $\geq 0.5 \geq 2 \geq 10$  ng/ml which means that systemic infection can not be excluded though they were negative for culture which agreed with Zahedpasha *et al.*, (2009) and Meisner, (2000) whom reported that sepsis is possible even when the culture was negative<sup>(50,51)</sup>. PCT results were statistically significant since ( $p \leq 0.05$ ) using chi-square which were illustrated in table (11) and figure (4).

PCT level of  $\geq 0.5$  ng/ml was accepted as pathological, PCT level of 0.5 -2 ng/ml, 2 -10 ng/ml and >10 ng/ml considered as weakly positive, positive and strongly positive respectively<sup>(51)</sup>.

When  $PCT < 0.5$  ng/ml, it means systemic infection (sepsis) is not likely. Local bacterial infection is possible. Low risk for progression to severe systemic infection (severe sepsis), while  $PCT \geq 0.5$  and < 2 ng/ml means systemic infection (sepsis) is possible. Moderate risk for progression to severe systemic infection (severe sepsis).  $PCT \geq 2$  and >10 ng/ml, means systemic infection (sepsis) is likely, unless other causes are known. High risk for progression to severe systemic infection (severe sepsis) and if  $PCT \geq 10$  ng/ml, it means that Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock. High likelihood of severe sepsis or septic shock (PCT in bacterial infections and sepsis)<sup>(49)</sup>. The different levels of PCT comparing color intensity of the test band with the color blocks of the reference card in our study are shown in figure (4).

Figure (5) shows the relationship between mortality and levels of PCT. The results showed that mortality rate according to PCT levels was (16%) /73 cases, and those cases were found in the levels  $\geq 2$  (7 cases) and  $\geq 10$  ng/ml (5 cases) which means that the neonate had reached either severe or septic shock. Patients whom their PCT results were at the level  $\geq 2$  died after 24-28 hours of sample collection while those with PCT level  $\geq 10$  died after 6-24 which means that the level of PCT may be related to the stages of sepsis (severe sepsis or septic shock).

Table (12) shows that The comparison between results of PCT with the results of CRP for the

same cases, the differences were statistically significant ( $p < 0.05$ ) using chi-square. PCT results for CRP-positive group were in accordance with CRP results 91% , While 3 cases of CRP-positive group were recoded as negative PCT ( $< 0.5$  ng/ml) { $< 0.5$  ng/ml means that sepsis is not likely} <sup>(27)</sup> .

As for CRP- negative group , the PCT results did not fitted with CRP results , four cases recorded higher level of PCT  $\geq 10$  ng/ml while they were negative for CRP. This result agreed with Sponholz, (2006) who reported that PCT is superior to C-reactive protein in discriminating infections <sup>(52)</sup> . Meisner, (2000) reported that induction of procalcitonin is infection related, but the immune consequences of infection (e.g. organ dysfunction) play a major role for the induction of this protein (CRP) <sup>(50)</sup> .

Table (13) shows that The comparison between results of PCT and WBC for the same cases performed. The differences were statistically significant ( $p \leq 0.01$ ). The table showed that 68% of cases were in the category of normal WBC range , while only 18% were in the category of leukocytosis and the rest of percentage were in the category of leucopenia agreed with Rudolph *et al.*, (2002) who stated that leukocytosis and neutrophilia are not good indicators of neonatal sepsis <sup>(11)</sup> .

Table (14) next page reveals the results of serum Procalcitonin measurements in comparison with ANC Results, shows that from all cases that performed PCT levels very few cases recorded neutropenia. The differences were highly significant ( $p \leq 0.01$ ) using Chi- square. WBC markers are specific ,but not very sensitive which means that a patient with sepsis may have normal WBC results <sup>(53)</sup> .

The statistical analysis of table (15) using analysis of variance (ANOVA) according to Duncun's Multiple Range in probability  $p \leq 0.05$  showed that the highest value was for PCT and the least values were for Elevated WBC, neutrophilia and leucopenia.

The percentage for each parameter differs from the other (table 15) . Blood culture had 46% sensitivity in our study, this might be due to several reasons e.g administration of antibiotics before blood collection or timing of culture did not precede the course of fever <sup>(24)</sup> . Rudolph *et al.*, (2002) stated that blood cultures are 82-90% sensitive in neonates , therefore with strong clinical suspicion of sepsis and an abnormal white cell count the infant may need to be fully treated with antibiotics even with negative blood cultures <sup>(11)</sup> .

Sensitivity for leukocytosis was only 15%, while leukopenia had 27 % , shift to left neutrophil had 58% sensitivity, neutropenia 16%, neutrophilia 18%. WBC markers are specific ,but not very sensitive which means that a patient with sepsis may have normal WBC results <sup>(53)</sup> . A recent study by Kofteridis *et al.*, (2009) showed that WBC elevation is neither sensitive nor specific indicator of bacteremia and other serious bacterial infection which is in agreement with our results since we got only 15% sensitivity for elevated WBC <sup>(54)</sup> .

CRP had a sensitivity of 36% disagreed with Jimenez *et al.*, (2009) who reported that CRP has a sensitivity of 78% for differentiating bacterial infection from other causes of SIRS <sup>(47)</sup> . Rudolph *et al.*, (2002) stated that CRP have low positive predictive accuracy and specificity for neonatal sepsis <sup>(11)</sup> .

lastly, sensitivity of PCT in the present study was 66% which proves that it could be used as a prognostic marker for diagnosis of sepsis better than traditional marker used in the present study agreed with Ivančević *et al.*, (2007) who found that, when PCT is compared with other routinely measured parameters such as WBC count, platelet count, or with CRP, PCT seems to be significantly more sensitive in sepsis diagnosis <sup>(46)</sup> .

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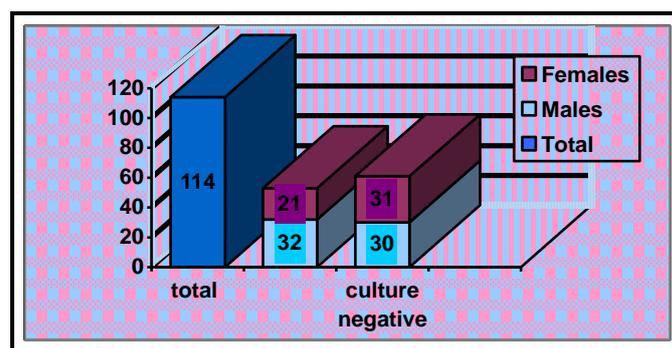


Figure 1 : Results of Blood Culture in Relation with Gender

Table 1 : Results of Identification for Bacterial Isolates

Bacterial Isolates	Number of isolates	%
<i>E. coli</i>	2	4
<i>P. aeruginosa</i>	3	6
<i>K. pneumoniae</i>	5	9
<i>C. diversus</i>	1	2
<i>S.marscesens</i>	1	2

<i>S. liquifascens</i>	1	2
<i>Nocardia spp.</i>	12	22
<i>Staph. aureus</i>	3	6
CONS	12	22
<i>L. monocytogenes</i>	9	17
<i>Lactobacillus spp.</i>	1	2
GAS	1	2
<i>Peptostreptococcus spp.</i>	1	2
<i>Micrococcus spp.</i>	1	2
Total	53	100

**Table 2 : Resistance Patterns of Gram Negative Bacterial Isolates**

Bacterial isolates	Antibiotics / No. of resistant isolates									
	E	RA	CIP	VA	AK	C	AM	CN	CTX	TE
<i>E. coli</i> (n=2)	2	2	2	2	2	2	2	2	2	2
<i>P. aeruginosa</i> (n=3)	3	3	1	3	1	2	3	3	3	3
<i>K. pneumoniae</i> (n=5)	5	5	5	5	1	1	5	4	5	5
<i>C. diversus</i> (n=1)	1	1	1	1	1	1	1	1	1	1
<i>S. marscesens</i> (n=1)	1	1	0	1	0	1	1	1	1	1
<i>S. liquifascens</i> (n=1)	1	1	1	1	1	0	1	1	1	1

n: number of total isolates  
E : Erythromycin RA: Rifampicin CIP: Ciprofloxacin CN: Gentamicin  
Am: Ampicillin VA: vancomycin CTX: Cefotaxime TE:Tetracycline  
AK: Amikacin C: Chloramphenicol

**Table 3 : Resistance Patterns of Gram Positive Bacterial Isolates**

Bacterial isolates	Antibiotics / No. of resistant isolates									
	E	RA	CIP	VA	AK	C	AM	CN	CTX	TE
<i>Nocardia spp.</i> n=12	12	10	0	0	2	6	11	0	11	1
<i>Staph .aureus</i> n=3	3	2	3	2	2	1	2	3	3	2
CONS n=12	12	9	7	10	7	6	10	8	10	7
<i>L. monocytogenes</i> n=9	6	9	5	5	2	5	9	0	9	3

<i>Lactobacillus sp.n=1</i>	1	0	0	-	0	1	1	0	0	0
GAS n=1	1	1	1	0	0	0	0	-	-	-

- : test for the antibiotic did not performed .

n: number of total isolates

E : Erythromycin RA: Rifampicin CIP: Ciprofloxacin CN: Gentamicin Am: Ampicillin  
VA: vancomycin CTX: Cefotaxime TE:Tetracycline  
AK: Amikacin C: Chloramphenicol

**Table 4 : Production of Some Virulence Factors Among Gram Negative Bacteria**

Isolates	No. of isolates	No. of isolates that produce				
		Hemolysin	Lecithinase	Lipase	Urease	Alkaline protease
<i>Nocardia spp.</i>	12	12	12	12	12	10
<i>S .aureus</i>	3	3	3	3	3	3
CONS	12	12	11	9	5	8
<i>L. monocytogenes</i>	9	9	9	9	1	8
<i>Lactobacillus spp</i>	1	1	1	1	1	1
GAS	1	1	0	0	0	0
Total	36	36(100%)	34(94%)	32(89%)	22(61%)	28(78%)

**Table 5 : Production of Some Virulence Factors Among Gram Positive Bacteria**

Isolates	No. of isolates	No. of isolates that produce				
		Hemolysin	Lecithinase	Lipase	Urease	Alkaline protease
<i>Nocardia spp.</i>	12	12	12	12	12	10
<i>S .aureus</i>	3	3	3	3	3	3
CONS	12	12	11	9	5	8
<i>L. monocytogenes</i>	9	9	9	9	1	8
<i>Lactobacillus spp</i>	1	1	1	1	1	1
GAS	1	1	0	0	0	0
Total	36	36(100%)	34(94%)	32(89%)	22(61%)	28(78%)

**Table 6: Distribution of Total WBC Count According to Culture Results**

	White Blood Cells cells/mm <sup>3</sup>		
	Leukocytosis ≥20,000 (%)	Normal range ≥ 6000≤ 20,000 (%)	Leukopenia ≤ 5000 (%)
Culture positive (n=52)100%	10(19)	25(48)	17(33)
Culture negative (n=50)100%	5(10)	32(64)	13(26)
<b>Total</b>	<b>102</b>	<b>15</b>	<b>57</b>

$X^2 = 3.021^* (p \leq 0.05)$

**Table 7 : Distribution of ANC Count in Relation with Culture Results**

	Absolute Neutrophil Count cells/mm <sup>3</sup>		
	neutrophilia > 7500- 8000cells	Normal range	Neutropenia < 1500cells/l
Culture positiven=52 (%)	10(19)	31(60)	11(21)
Culture negativen=50(%)	6(12)	35(70)	9(18)
<b>Total</b>	<b>16</b>	<b>66</b>	<b>20</b>

$X^2 = 1.404 \text{ n.s} (p \leq 0.05)$

**Table 8 : Distribution of CRP Results According to Culture Results**

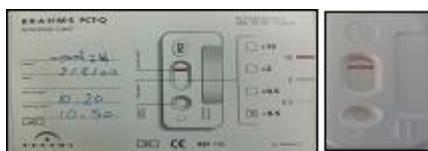
	C-reactive protein	
	Positive >6mg/l (%)	Negativ e<6mg/l (%)
Culture positive(n=3 9)100%	17(44)	22(56)
Culture negative(n= 45)100%	13(29)	32(71)
<b>Total</b>	<b>30</b>	<b>54</b>

$X^2 = 1.967 \text{ n.s}$

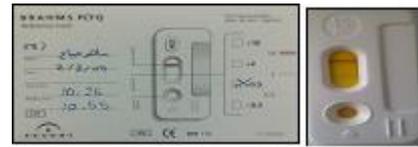
**Table 9 : Results of Serum Procalcitonin Measurements in Comparison with Blood Culture**

	Procalcitonin levels ng/ml			
	<0.5 (%)	≥0.5 (%)	≥2 (%)	≥10 (%)
Culture positive (n=38)100%	8(21)	14(37)	9(24)	7(18)
Culture negative negative(n=35)1 00%	17(49)	5(14)	8(23)	5(14)
<b>Total</b>	<b>73</b>	<b>25</b>	<b>19</b>	<b>12</b>

$X^2 = 7.785^*$



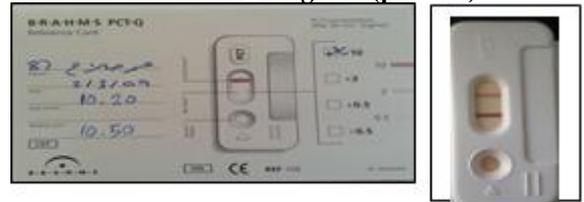
Picture A : < 0.5 ng/ml (negative)



Picture B: ≥ 5 l weekly positive accepted as pathologic)



Picture C: ≥ 2 ng/ ml (positive)



Picture D : ≥ 10 ng/ ml (strongly positive)  
Figure 2: Procalcitonin Results of Sera from Neonates with Suspected Sepsis

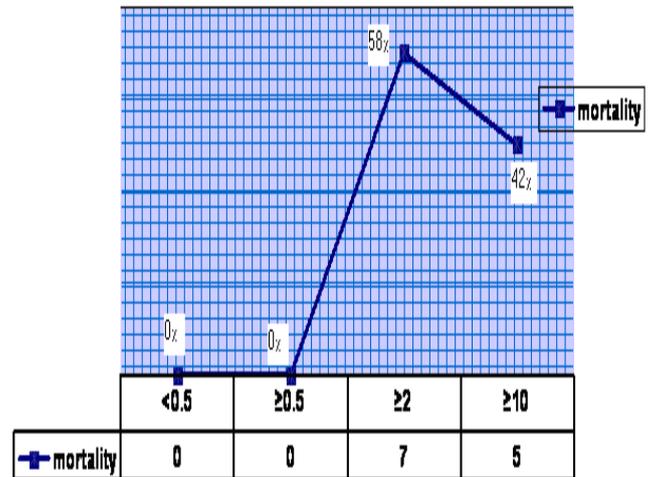


Figure 3 : Mortality Curve in Relation With PCT Levels

**Table 10 : Results of Serum Procalcitonin Measurements in Comparison with C-reactive protein**

	Procalcitonin levels ng/ml			
	<0.5 (%)	≥0.5 (%)	≥2 (%)	≥10 (%)
CRP- positive(>6mg/l)( n=32)100%	3(9)	12(38)	10(31)	7(22)
CRP- negative(<6mg/l)(n= 41) 100%	20(49)	9(22)	8(19)	4(10)
<b>Total</b>	<b>73</b>	<b>23</b>	<b>21</b>	<b>11</b>

$X^2 = 4.290^*$

**Table 11: Results of Serum Procalcitonin Measurements in Comparison with White Blood Counts**

	Procalcitonin levels ng/ml			
	<0.5 (%)	≥0.5 (%)	≥2 (%)	≥10 (%)
Leukocytosis(≥20,000cells/mm <sup>3</sup> ) (n=13)100%	2(15)	2(15)	2(15)	7(55)
WBC with normal range(n=49) 100%	20(41)	10(20)	12(25)	7(14)
Leukopenia (≤5000 cells/mm <sup>3</sup> )(n=11) 100%	1(9)	3(27)	7(64)	0
<b>Total</b>	<b>73</b>	<b>23</b>	<b>15</b>	<b>21</b>

X<sup>2</sup> = 19.598\*\*

**Table 12 : Results of Serum Procalcitonin Measurements in Comparison with ANC Results**

	Procalcitonin levels ng/ml			
	<0.5 (%)	≥0.5 (%)	≥2 (%)	≥10 (%)
Neutropenia (ANC<1500cells/mm <sup>3</sup> )(n=13)	4(31)	3(23)	5(38)	1(8)

100%				
Normal range of neutrophil count (n=47)100%	20(43)	12(26)	11(23)	4(8)
Neutrophilia (ANC> 7500-8000cells/mm <sup>3</sup> ) (n=13)100%	1(8)	2(16)	5(38)	5(38)
<b>Total</b>	<b>73</b>	<b>25</b>	<b>17</b>	<b>10</b>

X<sup>2</sup> = 14.699\*\*

**Table 13 : Sensitivity of Measurement Parameters**

Test	Total No.	Sensitivity of test %
Blood culture	114	46 c
Elevated WBC	102	15 f
Decreased WBC	102	27 e
Shit left neutrophill	102	58 b
Neutrpnesia	102	16 f
Neutrophilia	102	18 f
CRP	84	36 d
PCT	73	66 a

Duncan's Multiple Range in probability p<0.05

## تقييم اختبار البروكالسيتونين في التشخيص المبكر لتسمم الدم الجرثومي في الأطفال حديثي الولادة في مستشفى تكريت التعليمي

وعد محمود رؤوف ، موسى جاسم محمد ، عماد راشد السعدون ، سهى ماهر عبد الرشيد

### الخلاصة

إن تشخيص الخمج ضمن فئة حديثي الولادة يعتبر بحد ذاته تحدٍ , نظراً لكون الاختبارات التقليدية غالباً ما تؤدي إلى التضليل بدل التشخيص . صممت هذه الدراسة لأجل البتّ بإمكانية استخدام اختبار مستوى البروكالسيتونين كعلمٍ للتشخيص المبكر للحالات المشكوك بإصابتها بتسمم الدم الجرثومي في حديثي الولادة بالمقارنة مع زرع الدم , C-reactive protein , عدم خلايا الدم البيض الكلي والتفريقي . تم جمع 118 عينة دم اشتملت على كلا الجنسين خلال الفترة الزمنية من شهر آب سنة 2008 ولغاية شهر آذار سنة 2009 من حديثي الولادة الوافدين إلى ردهات الخدج والأطفال في مستشفى تكريت التعليمي والمخصصه سريريا من قبل طبيب الأطفال المختص على اشتباه اصابتهم بالمرض . أظهرت نتائج زرع الدم ان 53 (46%) من العينات كانت موجبه منها, 32 (60%) ذكور و 21 (40%) إناث . عدد حالات زرع الدم السالبة كانت 61 (54%) منها , 31 (51%) اناث و 30 (49%) ذكور . أظهرت نتيجة التشخيص المختبري بان العزلات البكتيرية الاكثر شيوعيا كانت من جنس البكتريا العقنوديه السالبة ومن *Nocardia spp.* لأنزيم التخثر بنسبة 22% لكليهما تتبعا بكتريا *Listeria monocytogenes* بنسبة 17% تليها *Klebsiella pneumoniae* بنسبة 9% و 6% لكل من *Pseudomonas aeruginosa* و *Staphylococcus aureus* أما باقي الأنواع ( *Citrobacter diversus*, *Serratia marscesens*, *Serratia liquifascens*, *Lactobacillus spp.*, *Peptostreptococcus spp.*, *Micrococcus spp.*, *Streptococcus pyogenes*) فقد كانت غير شائعة وأعطت نسب 2% لكل واحد . بينت هذه الدراسة أن حملة تسمم الدم الجرثومي المتأخر سجلت 67% من الحالات بينما الباقي من النسبة ( 33%) كان لحملة تسمم الدم الجرثومي المبكر . لقد كان عدد حالات التسمم الجرثومي المؤكد بين الذكور اعلى 32 ( 60 ) منه في الاناث 21 (40%) . أظهر اختبار فحص الحساسية ان عزلات البكتريا السالبة لصبغة جرام كانت ذات مقاومه عاليه للمضادات المستخدمة في الدراسة الحالية بينما كل عزلة من عزلات البكتريا الموجبة لصبغة جرام كان لها نمط مقاومه مختلف للمضادات . كما و

أظهرت الدراسة لعوامل الضراوة بان العزلات البكتيرية السالبة لصبغة جرام كانت موجبة لاختبار انتاج انزيم اليوريز و اختبار أنزيم الهيمولايسن و اختبار انزيم اللايبيز والسيثينيز والبروتيزينسبة 85% , 100% , 100% , 100% و 62% على التوالي بينما كانت العزلات الموجبة لصبغة جرام موجبة للاختبارات بنسبة 61% , 100% , 89% , 94% و 785 عالتوالي. اظهرت فحوصات الدم الروتينيه والتي كانت ذات قيمه معنويه بأن 33% من بين حالات زرع الدم الموجبة كان عدد خلايا الدم البيض فيها منخفض , 19% من الحالات كان عدد الخلايا البيض مرتفع اما باقي النسبة المؤية فقد كان نتيجة فحص عد خلايا ضمن المستوى الطبيعي. بالنسبة لفحص CRP كانت الفروقات الاحصائية غير ذات قيمه معنويه مابين الحالات الموجبه لزرع الدم عن الحالات السالبة . و فيما يخص نتيجة فحص PCT الذي تم قياسه باستخدام طريقة القياس شبة الكمي الكرماتوغرافيه المناعيه . أظهرت نتائج دراستنا أن 21% من حالات زرع الدم الموجبه اعطت مستوى بروكالسيتونين اقل من 0.5 نانوغرام لكل مل وباقي النسبة توزعت بين مستويات البروكالسيتونين الباقية  $10 \geq 2 \geq 0.5$ . بالنسبة لحالات زرع الدم السالبة فقد اظهرت نتيجة قياس مستوى PCT بان نسبة 49% كان ضمن مستوى البروكالسيتونين  $0.5 <$  نانوغرام لكل مل بينما 51% كانت ضمن المستويات  $2 \geq 0.5 \geq 10$  بمعنى لايمكن استبعاد حصول اصابة جهازيه حتى لو كانت نتيجة الزرع الدم سلبية. ومن مقارنة نتائج عد الخلايا البيض مع نتيجة البروكالسيتونين التي أجريت لنفس الحالات ظهر بان 68% من الحالات كانت ضمن معدل عدد الخلايا الطبيعي بالوقت الذي أعطت مستوى عالي للبروكالسيتونين  $10 >$  نانوغرام لكل مل و 18% فقط من الحالات كان عدد الخلايا البيض مرتفع وباقي النسبة اشتملت عل حالات انخفاض بها عدد الخلايا البيض عن الطبيعي . وعند مقارنة اختبار البروكالسيتونين مع باقي الفحوصات الروتينيه المستخدمه بالدراسه اتضح بانه اكثر حساسية في تشخيص تسمم الدم الجرثومي وفقا لذلك , نستنتج بان البروكالسيتونين هو محدد أكثر حساسية من الفحوصات التقليدية ( فحص زرع الدم وفحص أل CRP وفحص عد الخلايا البيض) في التشخيص المبكر لتجرثم الدم الناجم عن البكتريا عند الاطفال حديثي الولاده .