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Procalcitonin (PCT) as a promising marker for diagnosis and differentiation of bacterial infections

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Abstract
Background: *Bacteremia is a life-threatening infection whose prognosis is highly dependent on early recognition and treatment with appropriate antibiotics. Early identification of bacterial infection in patients with fever is important for prompt treatment. However, the available parameters such as C-reactive protein (CRP) and leukocyte counts are not very specific. This study was aimed to assess the diagnostic value of procalcitonin (PCT) and cholesterol for bacterial infection in febrile patients. Procalcitonin levels have been shown to distinguish between bacteremia and noninfectious inflammatory states accurately and quickly in critically ill patients. Also a decrease in plasma lipids occurs during severe sepsis and has prognostic implications in critical illness.*
Methods: *Review of the medical records of every patient treated between May, 2014 and May, 2015 who had bacteremia caused by either Gram positive (GP) or Gram negative (GN) bacteria, and whose PCT, WBCs, CRP and cholesterol levels were measured at the onset of infection*
Results: *88 episodes of either GN bacteremia (n = 56) or GP bacteremia (n = 32) were included. Procalcitonin levels were found to be markedly higher in patients with GN bacteremia than in those with GP bacteremia. TLC, CRP, PCT were significantly increased, while cholesterol was significantly decreased in cases when compared to control group.*
Conclusion: *In a critically ill patient with clinical sepsis, GN bacteremia could be associated with higher PCT values than those found in GP bacteremia, regardless of the severity of the disease. Low lipid levels, particularly low Cholesterol, pointed to bacterial infection Reflecting the severity of disease, plasma lipid levels may be a complementary tool in the diagnostic workup of patients with septicemia.*
Keywords: *Sepsis, Procalcitonin, C-reactive, protein, Bacteremia, cholesterol, WBCs.*

Introduction

Bacteremia is a life-threatening infection whose prognosis is highly dependent on early recognition and treatment with appropriate antibiotics (**Pierre et al, 2008**).

One of the most common causes of death in hospitalized patients is sepsis. In cases where sepsis is suspected, timely and adequate clinical decision making is required (**Dillinger et al, 2013**). The timely diagnosis of bacterial infections remains a challenge (**Schuetz et al, 2011**).

Fever has been seen as an early marker for infectious complications, although its positive predictive value for having an infectious complication has been questioned (**Niven et al, 2013**).

Also the combination of fever with other systemic inflammatory response syndrome criteria (tachycardia, tachypnoea and leucocytosis) is not very specific for infection and can occur in noninfectious conditions (**Meisner, 2013**).

The main disadvantages of many current microbiological methods are diagnostic delays, such as those that occur with culture methods, suboptimal sensitivity for samples like blood cultures, and low specificity due to contamination in samples likes sputum cultures, whereas others, such as lung biopsies, are not amenable to routine diagnostics due to their invasive nature.

Furthermore, inflammatory markers, including C reactive protein (CRP) and white blood cells (WBC), lack specificity for bacterial infections **(Muller et al, 2007)**.

During the last decades, there has been an ongoing search for the ideal marker of inflammation and infection; one that is fast, accurate and that can be determined at low cost, aiding well-judged and prompt treatment of patients suffering from an infection. With the rising incidence in antibiotic resistance, the development of a marker that would differentiate between inflammation and infection would make a much wanted more restrictive and targeted use of antibiotics possible **(Prkno et al, 2013)**.

Procalcitonin (PCT) has emerged as a promising marker for the diagnosis of bacterial infections because higher levels of PCT are found in severe bacterial infections relative to viral infections and nonspecific inflammatory diseases. Hence, PCT may be used to support clinical decisions regarding the initiation or discontinuation of antibiotic therapy **(Schuetz et al, 2012)**.

Procalcitonin is the prohormone of calcitonin and is synthesized by the C cells in the thyroid gland. It is produced ubiquitously in response to endotoxin or to mediators released in response to bacterial infections **(Pickkers, 2015)**. It is synthesized by a large number of tissues and organs in response to invasion by pathogenic bacteria, fungi, and some parasites **(Hyuck Lee, 2013)**.

Serum PCT is a 116-amino-acid peptide, and elevated levels of this peptide are strongly associated with systemic bacterial infections **(Christ-Crain M and Muller B, 2005).** PCT is useful not only for monitoring bacterial infections but also for the differential diagnosis of systemic inflammatory response syndrome, which is a serious medical condition **(Hyuck Lee, 2013)**.

PCT is markedly elevated (up to 5,000 fold) within 2 to 4 hours in severe forms of systemic inflammation or in bacterial infections **(Gilbert DN, 2010).** The biological half life of PCT is 22 to 26 hours, an advantageous time point compared with CRP and other acute-phase reactants **(Limper et al, 2010)**

The most useful application is the use of sequential PCT levels to determine when there is no longer a need for antibacterial therapy **(Manian FA, 2012)**.

Serum PCT measurement relies on a quick and routine lab test that has been reported to accurately differentiate between systemic bacterial infection and non-infectious acute inflammatory states, whereas white blood cells count (WBC) and serum C-reactive protein (CRP) failed to do so **(Shun Yuan Guo et al, 2015)**.

Moreover, it has been shown that the magnitude of PCT elevation closely correlates with outcome in critically ill patients **(Uzzan et al, 2006)**.

Nonspecific elevations in PCT levels in the absence of a bacterial infection can occur in situations of massive stress, such as after severe trauma and surgery or in patients with cardiac shock **(Aabenhus and Jensen, 2011)**.

Measurement of cholesterol levels could potentially be used as a cheaper, and valuable substitute for procalcitonin in this matter **(Biller et al, 2014)**.

Cholesterol is a reliable marker for daily follows up, to monitor improvement or deterioration of patients with infection. Evidence for infectious complications is important because the potentially evolving sepsis is associated with morbidity and[83] mortality **(Stevenson et al, 2014)**.

The serum lipid profile undergoes several changes during septic shock. It has been shown that cholesterol levels decrease during the acute phase whereas different subclasses as high density lipoprotein (HDL) also undergo an additional change in constitution **(Jahangiri, 2010)**. Recently even prognostic implications from low levels of HDL have been reported **(Lekkou et al, 2014)**.

This raises the question if cholesterol can be of help to guide ecisions about acute-phase responses when it is determined routinely every day. If so, cholesterol could be an adequate and cheap tool for monitoring treatment and could indicate improvement or deterioration of patients **(Biller et al, 2014).**

Materials and Methods

Adult patients (18 years or older) with symptoms of systemic infection and/or inflammation for whom a BC was obtained during the initial visit were enrolled in this study.

Stored blood specimens (serum or EDTA blood) for additional procalcitonin, cholesterol and other parameter analysis. Blood samples from serum-separator tubes were centrifuged, and an aliquot of the serum was removed and stored at −70°C for more assay. Clinical data were abstracted from the medical records and included age, sex, other criteria (WBC count, body temperature, blood pressure, and heart rate).

An episode of bacteremia or sepsis was defined as the recovery of any significant, pathogenic bacterial species in 1 or 2 sets of BCs (aerobic and anaerobic bottles) obtained. Organisms commonly considered as BC contaminants (eg, coagulase-negative staphylococci, aerobic and anaerobic diphtheroids, Micrococcus, and Bacillus sp) were excluded from this definition. BCs were processed using bactealert continuous BC monitoring system. Bacteria from positive BCs were further identified using vitek automated system. Cultures that did not indicate growth within 5 days of incubation were considered negative. Serum PCT concentration were measured by procalcitonin sandwitch ELISA technique (DRG), USA.

CRP was measured by immunospec hs CRP ELISA technique.

Results

A total of 88 patients (average age, 49.8 years) were enrolled; Overall, the bacteremia episodes were encountered in 51 males and 37 females.

Among the 88 bacteremia episodes, 56 were caused by GN and 32 by GP bacterial species.

The most frequent bacterial species encountered were Escherichia coli (n = 17), klebseilla (n = 11), proteus species (n = 4), and staph hemolyticus (n= 9) table(2).

In addition, the source of infection was mainly the abdomen (47.7%), the urinary tract (18.2%) and the respiratory tract (17%) table (3).

PCT median value of gram negative BCs (6.72ng/mL, IQR 1.5–23.3) was significantly higher than those observed in gram positive BCs (0.3ng/mL, IQR 0.1–0.9, and < 0.0001)

PCT median values according to BC results are shown in Figure 1.

PCT, CRP and cholesterol concentrations according to pathogen in patients with bacterial infection are shown in table (4).

Table (1): Comparison of demographic and laboratory data between studied groups.

		Control N=19		Cases N=88		*p*
Age (year)	Mean, SD	42.47	11.554	49.77	10.280	0.007
Gender; N, %	Males	15	78.9	51	58.0	0.088
	Females	4	21.1	37	42.0	
Total leucocytic count (X10^9/L)	Mean, SD	6.147	1.4335	16.649	2.2197	<0.001
Cholesterol (mg/dL)	Mean, SD	118.89	25.554	68.73	11.074	<0.001
CRP (mg/L)	Median, range	1.7	1-3	87	25-209	<0.001
PCT (ng/mL)	Median, range	0.02	0-0.1	13.3	0.9-96.3	<0.001

Cases mean age was 49.8 years, they comprised of 51 males and 37 females. In addition to control group of matched age and sex. TLC, CRP, PCT were significantly increased, while cholesterol was significantly decreased in cases when compared to control grou

Table (2): Patients' associated conditions.

Site of infection	N	%	Associated conditions	N	%
GIT	42	47.7	GE	17	19.3
			Peritonitis	13	14.8
			Cholycystitis	5	5.7
			Anorectal abscess	2	2.3
			Liver abscess	1	1.1
			Pancreatitis	1	1.1
			Hepatoma	3	3.4
GUT	16	18.2	UTI	15	17.0
			Renal tumor	1	1.1
Resp and cardiac	15	17	Pneumonia	10	11.4
			Nasosinusitis	1	1.1
			Endocardidtis	4	4.5
Others	7	8	Osteomylitis	3	3.4
			Typhoid fever	3	3.4
			Cellulitis	1	1.1
Unknown	8	9.1	Unknown focus	8	9.1

Table (3): Patients' microbiological data.

Gram	Positive					Negative					
Organism	N	%	Organism	N	%	Organism	N	%	Organism	N	%
Total	32	36.4				Total	56	63.6			
Co Neg Staph	20	22.7	Staph hemolyticus	9	10.2	E coli	17	19.3			
			Staph hominis	4	4.5	Klebsiella	11	12.5	K. pn	10	11.4
			Staph wareni	3	3.4				Kleb oxytoca	1	1.1
			Staph agalactea	1	1.1	Proteus	4	4.5			
			Staph lentus	3	3.4	Pseudomonas	3	3.4			
Staph aureus	1	1.1				Salmonella typhi	3	3.4			
Strept	3	3.4	Strept pn	1	1.1	Brucella melitensis	3	3.4			
			Strept mutans	1	1.1	Other G neg bacilli	17	19.3	Enterobacter cloaca	4	4.5
			Strept pyogenes	1	1.1				Enterobacter fecalis	3	3.4
Other G pos cocci	3	3.4	alloiococcus otitis	1	1.1				serratia marcescens	1	1.1
			kocuria kristinae	1	1.1				citrobacter koseri	1	1.1
listeria monocytogens	3	3.4							serratia ficaria	1	1.1
									aerococcus viridans	1	1.1
									aeromonas salmonicida	1	1.1
									leuconostoc mesenteroids	4	4.5
									sphingomonas paucimobilis	1	1.1
									achromobacter xylosoxidans	1	1.1

Table (4). Correlations of PCL with other studied parameters in all group.

	Control N=19		Cases N=88	
	r	*p*	*R*	*P*
Age (year)	.012	.961	.029	.790
Total leucocytic count (X10^9/L)	-.164	.502	.033	.762
Cholesterol (mg/dL)	.065	.792	-.162	.131
CRP (mg/L)	.399	.091	.337	.001

CRP was significantly correlated with PCL, otherwise, no significant correlations were found regarding PCL with other studied parameters in all groups.

Table (5). Comparison of demographic and laboratory data between Gram positive and negative organisms.

Gram		Negative N=56		Positive N=32		*p*
Age (year)	**Mean, SD**	49.59	10.228	50.09	10.526	0.826
Gender; N, %	**Males**	33	58.9	18	56.3	0.807
	Females	23	41.1	14	43.8	
Total leucocytic count (X10^9/L)	**Mean, SD**	16.795	2.1854	16.394	2.2908	0.418
Cholesterol (mg/dL)	**Mean, SD**	67.02	10.492	71.72	11.590	0.055
CRP (mg/L)	**Median, range**	91	25-209	61.5	27-204	0.001
PCT (ng/mL)	**Median, range**	39.6	3.8-96.3	4.7	0.9-16.5	<0.001

CRP and PCT showed significantly higher levels in Gram negative when compared to Gram positive organisms

Table (6). Regression analysis for prediction of infection in normal healthy controls.

	Univariate				Multivariate			
	P	OR	95% CI		*p*	OR	95% CI	
Age (year)	.449	1.005	.992	1.018				
Males		1						
Females	.629	1.073	.806	1.429				
Total leucocytic count (X10^9/L)	.010	1.047	1.011	1.085	.165	1.033	.987	1.082
Cholesterol (mg/dL)	.020	.992	.985	0.999	.392	.996	.987	1.005
CRP (mg/L)	.079	1.002	1.000	1.004				
PCT (ng/mL)	.252	1.003	.998	1.008				

Applying regression analysis for prediction of infection using age, gender, TLC, cholesterol, CRP and PCT as covariates. In univariate analysis, increased TLC and lower cholesterol were considered as predictors of infection. In multivariate analysis, applying variables which were significant in univariate analysis, none of these covariates were considered independent predictor for infection in studied cases.
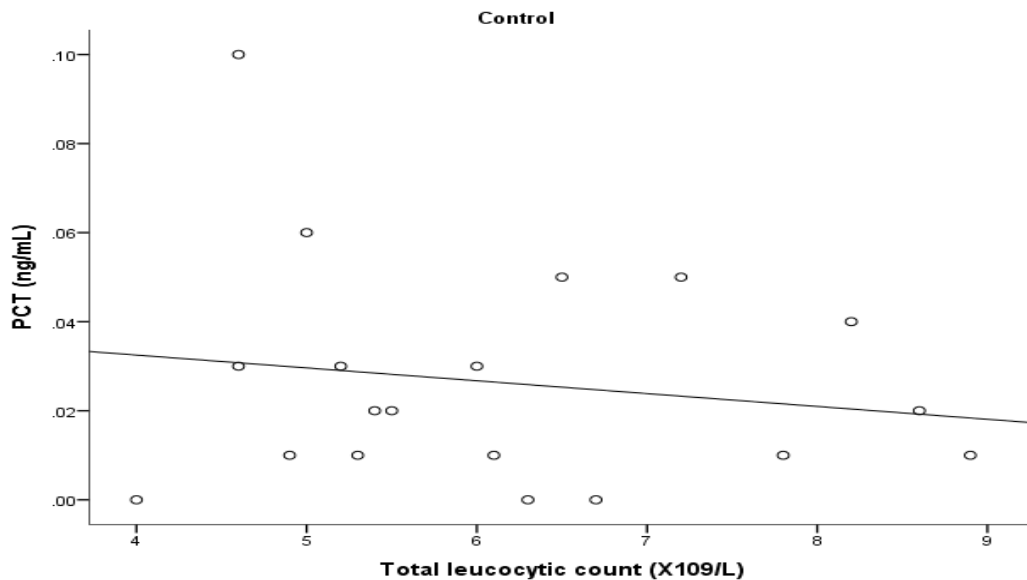
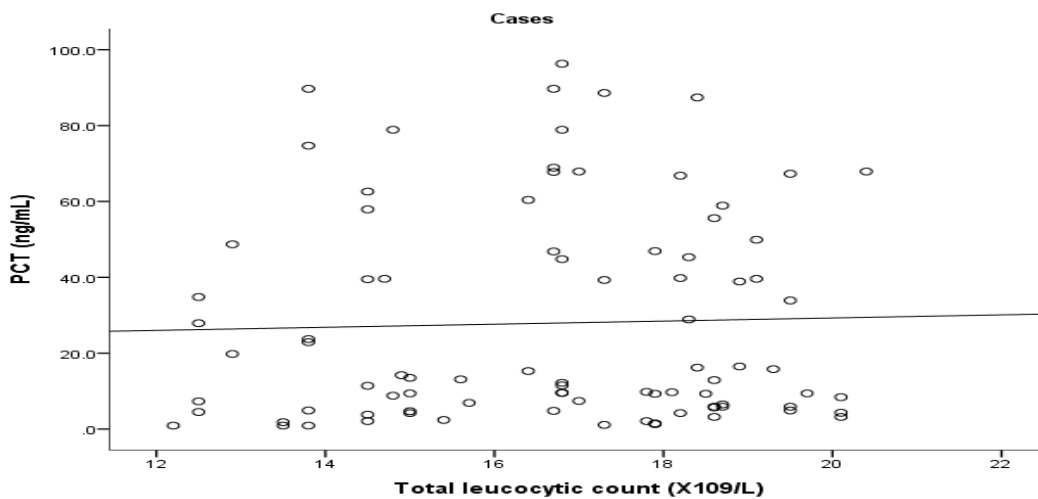**Figure (1).** Correlations of PCT with TLC in control group

Figure (2). Correlations of PCT with TLC in cases group

Discussion

Rapid detection of bacteremia facilitates early implementation of therapy and identifies patients at high risk for complications. (**Heper et al, 2006).** Previous studies demonstrated that various clinical markers have poor sensitivity and specificity for predicting early bacteremia in febrile patients (**Riedel et al, 2008)**.

Similarly, ruling out bacterial sepsis in febrile patients has substantial benefits, including reduction of hospitalization and antimicrobial use and facilitating clinician focus on alternative diagnostic pathways (**Lee et al, 2008).**

In the current study, we have focused on the rapid diagnosis of sepsis. We have assessed PCT and CRP as most commonly used markers and have looked for possible new markers as cholesterol level in bloodstream infections. Gram negative infections slightly dominated in our study (G negative in % cases and G positive in % cases).

In our study the most frequent pathogen notified was as in helena et al, 2012 study Staphylococci were identified as the most frequent causal pathogens in our cohort (33 %), followed by E.coli (16 %) and Klebsiella (14 %). In general, Staphylococci (i.e., Staphylococcus aureus) and Gram-negative rods from family Enterobacteriacea are the most common causative agents of sepsis. On the other hand, isolation of

coagulase negative staphylococci is frequently a consequence of contamination of blood samples. In patients with Escherichia coli, Klebsiella spp, and Pseudomonas spp. In vitro studies have clearly described the functional differences of G negative G positive organisms invading the human host.

Thus, it was shown that the involvement of Toll-like receptors in the whole blood response to various bacterial pathogens was highly variable and depended on the composition of their outer membrane.

Composition of the outer membrane is one of the main determinants of the Gram stain result. The magnitude of the cytokine response was thus found to depend on the invading pathogen. More precisely, it has been shown that the Tumor necrosis factor-α (TNF-α) plays a pivotal and very proximal role in the cytokine response to bacteria.

However, plasma TNF-α is not necessarily high whatever the causative microorganism may be (**Karlsson et al, 2004).** Given the critical role of this cytokine in the release of PCT from various cell lines in the context of systemic bacterial infection, the magnitude of the PCT elevation could be, at least in part, related to the characteristics of the pathogen

Abe et al. 2010 affirmed that G- bacteremia induces greater magnitude of inflammatory response than G+ bacteremia.

And this may be the answer for a higher elevation levels of PCT in G- bacteremia, as described by Feezor and Charles (**Charles et al., 2008**). Charles also concluded that G- bacteremia could be associated with higher PCT values than those found in GP bacteremia, regardless of the severity of the disease.

(**Charles et al., 2008**).

But why CRP is not higher at the same time in G- is hard to say. Hence, PCT levels could serve as a simple utility for confirmation or exclusion of G- bacterial septicemia in these groups of patients. Our findings are in line with observations of Montagna et al ,2011. Generally, PCT is more specific marker for infection than CRP (ROC analysis), and CRP has good sensitivity but less specificity (Reinhart K and Meisner M (2011)) Also the physiological role of both markers is not the same. We actually do not know how it works exactly. Each marker is slightly different PCT could be considered as a good discriminative biomarker in different bloodstream infections.

In the present study, we found that procalcitonin is a promising candidate marker for rapid detection of BSI. In this study of patients recruited from the ED setting, using BC result as the gold standard, we found that procalcitonin levels are dramatically different in patients with and without bacteremia, consistent with previous reports (**Vorwerk et al, 2009)**

Because procalcitonin results are available long before BC results, procalcitonin results not only can be an important screening tool to rule out bacteremia but also will further assist in the retrospective assessment of BC results when perhaps only 1 or 2 sets of BCs are positive for organisms known to be potential contaminants.

Since PCT elevation is deemed to depend directly on inflammatory mediators released by the host in response to the offending pathogen, a different pattern of response could account for such differences. This hypothesis is supported by the fact that GP and GN bacteria are known to elicit inflammatory responses that rely on different signaling pathways of the innate immunity network. This has recently been illustrated in the compartment (**Elson et al, 2007).**

It has been shown in vitro that PCT peak value was significantly higher in the supernatants of cultured human cells stimulated with LPS(Lipopolysaccharide) than in those stimulated with muramyl dipeptide, a component of the outer membrane of the Gram positive bacteria (**Tavares et al, 2005).**

Since PCT measurement is available sooner than the Gram stain result, its value could be considered when discussing the choice of first line antibiotics in critically ill patients with clinical sepsis.

Besides, CRP was also found to be of value in detecting bacterial infection in febrile patients.

Previous studies have also used CRP level to identify bacterial infections in febrile patients (**Lee et al, 2012**) and PCT was superior to CRP in identifying bacterial infection.

Though CRP is the most commonly measured acute parameter in infection and sepsis, it is not a reliable marker in identifying bacterial infection because of its low sensitivity and specificity (**De Kruif et al, 2010).** A previous study showed IL-6 as a better prognostic marker of bacterial infection than CRP in patients with febrile neutropenia (**von Lilienfeld-Toal et al, 2004).** This inconsistency may be due to different testing time. In addition, there was no significant association between PCT and CRP which also might be related to the different peak time and plasma half-life of different biomarkers after a stimulus. PCT increases in blood six hours after a stimulus, reaches a plateau between 12 and 48 h, and then decreases if the stimulus stops.

CRP increased four hours later than PCT(**Limper et al, 2010).** In general, biomarker measurement has some disadvantages.

Probably the combination of biomarkers would lead to a better sensitivity and specificity to predict bacterial infections. Our study showed that PCT levels in Gram-negative bacterial infections were significantly higher than that in Gram-positive bacterial infections, consistent with results of previous studies (**Prat et al, 2008**)[.]

When looking into our own database and comparing cholesterol, CRP and procalcitonin to the clinical courses of our patients, we have the impression that, as shown above, there is a correlation between cholesterol and the other[275] inflammatory parameters.

Moreover, there seems to be an association between cholesterol and the clinical course. Cholesterol has been known to be associated with the severity of disease. Research is focusing on the explanation of the decrease in the separate subclasses of cholesterol and its meaning in view of severe[281] sepsis (**Biller el al, 2014**).

Total cholesterol, which we measured in our study, can be divided into low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides which are mainly transported through the blood by very low-density lipoprotein (VLDL) cholesterol. During severe sepsis, LDL cholesterol reaches its minimum early in the course of the disease. This decrease is thought to be due to a diminished synthesis and efflux of cholesterol from the liver (Chen et al, 2012).

Although, in general, decreasing cholesterol was accompanied by an increasing CRP and procalcitonin, it did not always do this in the same timeframe or with the same tenacity.

In the presented graphs cholesterol seems to be a parameter to monitor the overall clinical condition of the patient, i.e. it seems to be a marker for overall deterioration or improvement.

Compared with CRP, cholesterol levels seem to change a bit earlier in the clinical course than CRP levels do. Like CRP, cholesterol is not a specific marker for infection. Determining cholesterol involves about10 times cheaper than C-reactive protein and about 500 to 600 times cheaper than procalcitonin. We, therefore, think that cholesterol may be a promising cheap and early marker for daily follow-up of patients with sepsis. In our view it can be a valuable addition to other parameters in determining the course of these patients, although further studies are needed (**Kreeftenberg et al, 2015**).

Therefore, we investigated the possible role of cholesterol levels as a prognostic marker on the first day of admission to the intensive care unit because cholesterol levels have been reported to be of prognostic value irrespective of the underlying disease in a large population of hospitalized patients (**Chiarla et al, 2010**).The underlying mechanisms for the rapid fall of cholesterol are still unclear. Probably increased demand of cholesterol as well as impaired synthesis due to liver dysfunction may account for this decrease (**Chiarla et al, 2010**).

In our study, cholesterol decrease has a prognostic value only in patients with infection but not in patients without infection.

These data support the hypothesis that circulating lipoproteins, such as LDL or HDL, which carry more than 90% of circulating cholesterol, may play a protective role during infectious disease. In vitro studies

demonstrated that lipoproteins bind to the bioactive lipid a portion of LPS, thereby decreasing the bioavailability of this toxin to various endotoxin responsive cells (Berbe´e et al, 2005).

The exact pathophysiological mechanisms underlying hypocholesteraemia in severe illness and sepsis have never been fully understood (Grubera et al, 2009).

Different mechanisms, including imbalance between synthesis and utilization of plasma lipids, usage of lipids to restore damaged cell membranes, and interaction of cytokines and bacterial toxins with lipids, have been discussed. Clinical and experimental studies demonstrated that high circulating levels of cytokines decrease cholesterol levels during severe infection (Murch et al, 2007).

Conclusion

There is a lot more to learn about PCT. The use of PCT, like any biomarker, should be considered within the context of the clinical workup and should take into account all patient related and therapy related factors that may interfere with the initial magnitude and course of this parameter.

In conclusion, PCT may be a valuable biomarker of bacterial infections in febrile patients, with greater predictive value than CRP and other biomarkers of infection.

For Ethical Requirements

1- We obtained a written consent from patients involved in this work.
2- There is no conflict of Interest between any one of the authors.
3- The research work is not funded.

References

1. Pierre Emmanuel Charles, Sylvain Ladoire, Serge Aho, Jean Pierre Quenot, Jean-Marc Doise, Sébastien Prin, Niels-Olivier Olsson and Bernard Blettery ;Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either gram negative or gram positive bacteria BMC Infectious Diseases 2008, 8:38 doi:10.1186/1471-2334-8-38

2. Dillinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guideline for management of severe sepsis and sepsis shock, 2012. Crit Care Med 2013;41:580–637.

3. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions past, present and future. BMC Med 2011;9:107.

4. Muller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 2007;7:10.

5. Hyuck Lee Korean J Procalcitonin as a biomarker of infectious diseases Intern Med 2013;28:285-291

6. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis 2012;55:651-662.

7. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G. An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients.Intensive Care Med 2012;38:940-949.

8. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med 2011;9:107

9. Helena Brodska´• Karin Malı´cˇkova´• Va´clava Ada´mkova• Hana Bena´kova´ • Marke´ta Markova´ Sˇtˇastna´• Toma´sˇ ZimaSignificantly higher procalcitonin levels could differentiate Gramnegative sepsis from Gram-positive and fungal sepsis Clin Exp Med-012-0191-8 2012

10. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. J Clin Microbio 2010;48:2325-2329.

11. Limper M, de Kruif MD, Duits AJ, Brandjes DP, van Gorp EC. The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from noninfectious fever. J Infect 2010;60:409-416

12. Manian FA. Use of procalcitonin to guide duration of antimicrobial therapy in intensive care units: proceed with caution. Clin Infect Dis 2012;54:578.

13. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 2007;7:210-217

14. Aabenhus R, Jensen JU. Procalcitonin-guided antibiotic treatment of respiratory tract infections in a primary care setting: are we there yet? Prim Care Respir J 2011;20:360-367.

15. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH: The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000, 118:146-155.

16. Christ-Crain M, Muller B: Procalcitonin in bacterial infections hype, hope, more or less? Swiss Med Wkly 2005, 135:451-460.

17. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY: Procalcitonin as a diagnostic test for sepsis in critically ill adults and aftersurgery or trauma: A systematic review and meta-analysis. Crit Care Med 2006, 34:1996-2003.

18. Shun Yuan Guo, MD, Yin Zhou, MD, Qing Feng Hu, PhD, Jiong Yao, PhD and Hong Wang, MD in Patients With Sepsis Procalcitonin Is a Marker of Gram-Negative Bacteremia The American Journal of the Medical Sciences Volume 349, Number 6, June 2015

19. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a system review and meta-analysis. Lancet Infect Dis 2013;12:70323–7.

20. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock – a systematic review and meta-analysis. Crit Care. 2013;17:R291.

21. Biller K, Fae P, Germann R, Drexel H, Walli AK, Fraunberger P. Cholesterol rather than procalcitonin or C-reactive protein predicts mortality in patients with infection. Shock. 2014;42:129-32.

22. E. Ewalds, P. Pickkers. Cholesterol as an inflammatory marker: cheap but valuable? NETH J CRIT CARE - VOLUME 20 - NO 2 - APRIL 2015

23. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med. 2014;42:625-31.

24. Niven DJ, Stelfox HT, Shahpori R, Laupland KB. Fever in Adult ICUs: an interrupted Time Series Analysis. Crit Care Med. 2013;41:1863-69.

25. Meisner M. Current status of procalcitonin in the ICU. Neth J Crit Care. 2013;17:4-12.

26. Jahangiri A. High-density lipoprotein and the acute-phase response. Curr Opin Endocrinol Diabetes Obes. 2010;17:156-60.

27. Lekkou A, Moukzaki A, Siagris D, et al. Serum lipid profile, cytokineproduction, and clinical outcome in patients with severe sepsis. J Crit Care 2014;29:723-7

28. Biller K, Fae P, Germann R, Drexel H, Walli AK, Fraunberger P. Cholesterolrather than procalcitonin or C-reactive protein predicts mortality in patients with infection. Shock. 2014;42:129-32.

29. Heper Y, Akalin EH, Mistik R, et al. Evaluation of C-reactive protein, procalcitonin, tumor necrosis factor alpha, and interleukin-10 levels as diagnostic and prognostic parameters in patients with

community-acquired sepsis, severe sepsis, and septic shock. Eur J Clin Microbiol Infect Dis. 2006;25:481-491.

30. Riedel S, Bourbeau P, Schwartz B, et al. Timing of specimen collection for blood cultures from febrile patients with bacteremia. J Clin Microbiol. 2008;46:1381-1385.

31. Lee CC, Chen SY, Tsai CL, et al. Prognostic valueof mortality in emergency department sepsis score,procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. Shock. 2008;29:322-327

32. Karlsson H, Larsson P, Wold AE, Rudin A: Pattern of cytokine responses to gram-positive and gram-negative commensal bacteria is profoundly changed when monocytes differentiate into dendritic cells. Infect Immun 2004, 72:2671-2678.

33. Abe R, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Tateishi Y(2010) Gram-negative bacteremia induces greater magnitude ofinflammatory response than gram-positive bacteremia. Crit Care14:R27

34. Charles PE, Ladoire S, Aho S, Quenot JP, Doise JM, Prin S (2008) Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either gram negative or gram positive bacteria. BMC Infect Dis 8:38

35. Montagna MT, Coretti C, Caggiano P (2011) Procalcitonin: a possible marker of invasive fungal infection in high risk patients?

36. J Prev Hyg 52:38–39Reinhart K, Meisner M (2011) Biomarkers in the critically ill patient: procalcitonin. Crit Care Clin 27:253–263

37. Vorwerk C, Loryman B, Coats TJ, et al. Prediction of mortality in adult emergency department patients with sepsis. Emerg Med J. 2009;26: 254-258.

38. Elson G, Dunn-Siegrist I, Daubeuf B, Pugin J: Contribution of tolllike receptors to the innate immune response to gram-negative and gram-positive bacteria. Blood 2007, 109:1574-1583.

39. Tavares E, Maldonado R, Ojeda ML, Minano FJ: Circulating inflammatory mediators during start of fever in differential diagnosis of gram-negative and gram-positive infections in leukopenic rats. Clin Diagn Lab Immunol 2005, 12:1085-1093.

40. Lee CC, Hong MY, Lee NY, Chen PL, Chang CM, Ko 23. WC. Pitfalls in using serum C-reactive protein to predict bacteremia in febrile adults in the ED. Am J Emerg Med 2012; 30 : 562-9

41. de Kruif MD, Limper M, Gerritsen H, Spek CA, Brandjes 8. DP, ten Cate H, et al. Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department. Crit Care Med 2010; 38 : 457-63.

42. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, Lehmann 25. L, Breig P, Hahn C, et al. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: procalcitonin and IL-6 are more reliable than C-reactive protein. Eur J Clin Microbiol Infect Dis 2004; 23 : 539-44..

43. Limper M, de Kruif MD, Duits AJ, Brandjes DP, van Gorp 7. EC. The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever. J Infect 2010; 60 : 409-16.

44. Prat C, Sancho JM, Dominguez J, Xicoy B, Gimenez M, Ferra 31. C, et al. Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leuk Lymphoma 2008; 49 : 1752-61.

45. Biller K, Fae P, Germann R, Drexel H, Walli AK, Fraunberger P. Cholesterol rather than procalcitonin or C-reactive protein predicts mortality in patients with infection. Shock. 2014;42:129-32.

46. Chen Y, Zhao L, Chen Y, et al. Inflammatory stress exacerbates hepatic cholesterol accumulation via disrupting cellular cholesterol export. J Gastroenterol Hepatol. 2012;27:974-84.

47. Cholesterol in the ICU: a cheap and reliable marker for illness severity? H.G. Kreeftenberg 1, A.N. Roos 1, A.J.G.H. Bindels 1, V. Scharnhorst 2 NETH J CRIT CARE - VOLUME 20 - NO 2 - APRIL 2015

48. Chiarla C, Giovannini I, Giuliante F, Zadak Z, Vellone M, Ardito F, Clemente G, Murazio M, Nuzzo G: Severe hypocholesterolemia in surgical patients, sepsis, and critical illness. J Crit Care 25:361, 2010.

49. Berbe´e JF, Havekes LM, Rensen PC: Apolipoproteins modulate the inflammatory response to lipopolysaccharide. J Endotoxin Res 11:97Y103, 2005.

50. Maja Grubera, Mirjam Christ-Craina, Daiana Stolzc, Ulrich Kellera, Christian Müllerb, Roland Bingisserb, Michael Tammc, Beat Muellera, d, Philipp Schuetza SWiSS Med Wkly Prognostic impact of plasma lipids in patients with lower respiratory tract infections – an observational study 2 0 0 9; 13 9 (11 – 12): 16 6 – 17 2

51. Murch O, Collin M, Hinds CJ, Thiemermann C. Lipoproteins in inflammation and sepsis. I. Basic science. Intensive Care Med.2007; 33:13–24.