Sepsis

Chapter 1

The Role of Procalcitonine in Septic Patients

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1. Introduction

Sepsis is a life threatening disease causing millions of deaths worldwide every year [1-7]. It is caused by the systemic immune response after a severe infection, more often from bacteria, but also from fungi, viruses and parasites [3,8]. The definition of sepsis which includes SIRS + proofs or suspicions of an infection, can be very wide and includes a lot of patients that does not have to develop sepsis [2,6,9]. During sepsis, the microorganisms invade to the bloodstream, and directly proliferate locally and release various virulent factors into the bloodstream [3,10,11]. In the diagnostic process of identifying an infection, one of the most important steps is the analysis of laboratory biomarkers of infection. The biomarkers, such as, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), reactive C-protein (CRP) and procalcitonin (PCT) can be used to help in the diagnosis, therapeutic monitoring and the risk classification. However, these blood parameters are not sensible or specific in the differentiation of an inflammation caused by a bacterial infection, from that caused as a response to a surgical damage. WBC, CRP and interleukin-1 (IL-1) are conventional markers used for the diagnosis of sepsis [5,6,12-14]. In this context, serum procalcitonin (PCT) has been a sensible biomarker that provides information for the prognosis in the patients with infections and so can improve the management of sepsis [5]. Compared to CRP, PCT has better

diagnostic and prognostic value and will differentiate without doubts a viral from a bacterial infection [6,9,15,16]. PCT is a diagnostic marker of severe bacterial infections and sepsis. The measurement of PCT is being accepted worldwide during this late decade. The plasmatic concentration of PCT increases very fast (6-12 hours) after an infection has caused a systemic response. Besides that, PCT plasma concentration level is indirectly related to the severity of sepsis and the systemic inflammatory reaction, and PCT plasma elimination half-life of about day gives indications of the course of the disease and the success of therapy [10,16,17]. Anyway, biomarkers should be used always in correlation with a full clinical, laboratory and radiologic evaluation, and with a perfect knowledge of the biology, benefits and limitations.

2. Measurement of PCT

In 1975, Moya F et.al. Suggested the existence of a precursor for calcitonin in chicken. The large biosynthetic molecule splits intracellularly to generate the hormone that was called procalcitonin [15,18]. The following studies show that calcitonin is secreted after a continuous Co and posttranslational modification, for example, like the glycosylation protiolytic cleavage, etc. [1,4,5,11,19-21]. In healthy individuals, PCT is produced in C cells of thyroid gland, from a gene called CALC-1 located in chromosome 11. PCT is a precursor of the hormone calcitonin and is synthesized physiologically by thyroid C cells (10). Procalcitonin is a 116 aminoacid peptide that has approximately 14.5 kDa and belongs to the superfamily of peptic calcitonins (CT). It can separate in three sections including the amino-terminus of PCT section, immature calcitonin and calcitonin carboxyl-terminus peptid-1 (CCP-1, named also catacalcin) [7]. The expression of procalcitonin is tissue specific. In the absence of infection, the transcription of CALC-1 gene to PCT is blocked in non-neuroendocrine tissues, besides C cells of thyroid gland, where its expression produces PCT, the precursor of CT in healthy and noninfected individuals [5]. The synthetized PCT undergoes a post-translational modification to produce small peptides and mature CT, which is generated as a result of the cleavage from peptidylglycine α-amidating monooxygenase (PAM) of C-terminal glycine from the immature CT. In the presence of a microbial infection, the non-neuroendocrine tissues express also the CALC-1 gene to produce PCT. A microbial infection causes considerable increase of expression of CALC-1 genes in all the parenchymal tissues and the cells differentiated to produce PCT. Its levels increase considerably during severe systemic infections, in comparison to other microbial infection parameters. The function of PCT synthetized in non-neuroendocrine tissues after a microbial infection is actually not clear; however, its discovery has helped in the differentiation of the diagnosis of inflammatory processes. In bacterial septicemia, PCT is produced by an alternative pathways, directly or indirectly [15]. PCT increases notably (up to 5000 fold) within 2 to 4 hours in the severe forms of systemic inflammation or in bacterial infections and its level continues until improvement [22,23]. The biologic half-life of PCT is 22 up to 26 hours, a favorable point in comparison to CRP and other markers of acute phase [24]. Differently from

CRP and the other markers of acute phase, the existing data suggest that the level of PCT rarely increase in response to viral infections. This shows that PCT can be valuable in the distinction of bacterial from viral infections. The predictive value of PCT is tested in some studies and in a recent multicentric study [25].

3. The Benefits of Procalcitonin

Procalcitonin (PCT) is widely considered as the most useful marker of severe systemic inflammation. Procalcitonin is normally present in the blood at low levels. However, its production can be stimulated from inflammatory cytokines and bacterial endotoxins, causing its release in higher amounts as a response to infection and, specifically, in systemic bacterial infections [6,12,19,21]. Procalcitonin is described for the first time in the early 1990s, as an induced protein in sepsis discovered in the plasma of the patients with sepsis and infection [20]. Since then procalcitonin is defined as a mean to differentiate bacterial infection from other inflammatory or infectious processes [1,4,7,10,15,17,19,21,26-28]. In comparison to all the other markers actually evaluated in sepsis, PCT seems to have also the potential to differentiate systemic infectious from noninfectious inflammation [12]. The levels of procalcitonin serve as a biomarker of inflammatory reaction, providing an indicator of the risk for sepsis: the higher the level of PCT, the higher the possibility of the presence of a systemic infection and sepsis. Keeping in mind the high sensitivity towards most types of infections, procalcitonin is considered widely as the most sensitive biomarker to help in the diagnosis (or exclusion) of bacterial sepsis. The international guidelines recommend its use during the treatment with antibiotics. Procalcitonin has a shorter half-life than CRP and the levels of PCT increase faster in bacterial infections. The levels of PCT are used to guide the empiric antibacterial therapy in patients with exacerbation of chronic bronchitis, community acquired pneumonia (CAP) and sepsis [17,28-32]. PCT is useful not only for monitoring the bacterial infections, but also in the differential diagnosis of SIRS, which is also a serious health condition in daily practice. Probably, PCT has other functions, besides signaling a bacterial invasion, which need further studies [5,11,16]. Another use of PCT in febrile patients is the differential diagnosis of an infection of the lower urinary tract and pyelonephritis, with a upper cutoff of 0,5 up to 1 ng/mL. In a last meta-analysis, the values >0.5 ng/mL suggest involvement of the renal parenchyma. That is why, PCT is included in the several guidelines [14,25,29]. These elements can make possible the early diagnosis of sepsis and monitor better its progression. Procalcitonin (PCT) is a promising marker for the early diagnosis of bacterial infections, because the high levels of PCT are found in severe bacterial infections in comparison to viral infections and nonspecific inflammatory diseases [22].

4. Procalcitonin and Bacterial Infection Diagnosis

Procalcitonin seems to have higher sensitivity and specificity than CRP in the diagnosis

of IBI. PCT is a promising marker to differentiate bacterial infections from other types of infection, including neutropenic fever, mycotic infections, postoperative fever, arthritis and suspected bacteremia [8,17,28,33,34]. The multicentric study from Lopez et al. showed that in an emergency department, PCT allowed an early diagnosis of invasive blood infection (IBI) in babies with fever in comparison to CRP. The authors considered IBI as a contagious disease that is confirmed by specific cultures: meningitis, sepsis, bone or joint infections (the local isolation of the microorganism or in blood culture), acute pyelonephritic infections, lobar pneumonia, bacterial enteritis in infants under 3 months and occult bacteremia [11,35,36]. In the cases with sepsis, Rey et al. demonstrated similar results. Another important factor suggested by Rey was the possibility to classify the patient according to the severity utilizing PCT: the higher the value of PCT, the more severe the sepsis [37]. Every type of infection, including pneumonia, urinary tract infections (UTI) and superficial surgical infections (SSI) should improve during perioperative period. That is why it is important to discover every infection during the perioperative period, in order for to start quickly the appropriate antimicrobial therapy [27]. In CNS infections, it is noted a disturbance of the brain-blood barrier (BBB) in patients with bacterial infections and in experimental models. Above it is mentioned that the levels of PCT in serum increase during bacterial, parasitic or fungal infections, but remain normal or increase slightly in viral infections and noninfectious inflammatory reactions [38-40]. The high levels of PCT in CSF in patients with bacterial meningitis seem to be a result of this mechanism and some studies have showed higher levels of PCT in CSF in patients with Gram-negative bacteria compared to patients with Gram-positive bacteria. In cases of CSN infection, the cells of microglia and meninges express receptors (similar to Toll-in [TLRs] receptors) against invading bacteria. A lot of questions related to the synthesis and secretion of PCT from brain cells during bacterial meningitis have not yet had an answer and need further investigations [11,41-47].

5. Correlation of PCT with the Severity of Sepsis

PCT as a biomarker showed its clinical usefulness in the verification of the presence of sepsis. Moreover, it correlates with the amount and severity of microbial invasion [15,30,48,49]. PCT is useful in clinic and is superior compared to other laboratory tests in the diagnosis of sepsis. It is directly related to the extension and severity of microbial invasion [48,50,51]. In contrast to other diagnostic biomarkers, including CRP, the studies in animals have shown strong evidence that PCT plays a physiopathologic role in the development of severe sepsis and in the mortality related to sepsis. PCT corresponds with the extension and severity of infection and has prognostic value, because the levels of PCT predict the risk of mortality in patients with severe infectious diseases and in patients with pneumonia on mechanical ventilation [48,52]. PCT sensitive analysis are necessary to make a reliable diagnosis of respiratory tract infections (RTIs) of CAP and nonCAP. Two low measurements of PCT, during the first 4-6

hours of hospitalization, resulted in less patients started on empirical antibiotic therapy. The low levels of PCT during the first 4 hours of hospitalization have an excellent negative predictive value for bacterial infections. In patients with severe systemic inflammation, severe sepsis and multiorgan disfunction, PCT has showed to be a wide specter parameter and clinically useful, being the best parameter to evaluate the severity, prognosis and disease course [6,53]. PCT kinetics may aid in the differential diagnosis between true sepsis and the normal inflammatory response to burn trauma in the first days after burn injury [19,45,54].

6. PCT for Antibiotic Guidance in other Infections

PCT helps to start and/or stop the administration of antibiotics in children and adults, which have different infections and different features, from primary care in the emergency department, to the hospital wards and intensive care units (ICU) [55-57]. It is utilized for the guidance of antibiotic therapy in infections of respiratory tract. When the clinical signs improved and the level of PCT went <35% of its initial value, the treatment with antibiotics was interrupted in the patients that were monitored with PCT. It was noted that the algorithm based in PCT, increases the utilization of antibiotics and also the treatment costs [15]. While the levels of PCT increase after a bacterial infection and decrease after recovery, they can be used to guide antibiotic therapy in individual patients as a surrogate biomarker. For some infections, PCT may not be enough sensitive for the use in clinical routine. In patients with subacute endocarditis, the levels of PCT can be low and cannot be used to differentiate infected from noninfected patients. In a similar way, in patients with Mycoplasma or viral infection, the levels of PCT can remain low, while in other atypical pathogens like Legionella pneumophila, PCT shows a significant increase after infection. The algorithm for PCT can be used to decide the treatment with antibiotics in the cases with perforation of gastrointestinal tract and helps reduce the course of antibiotics [58].

7. Antibiotic Stewardship with PCT

Antimicrobial resistance is a main factor that influences the prognosis of a patient. This requires strict efforts to reduce the exaggerated use of antibiotics [30,58]. A lot of variations are reported. In the cases of “alarm PCT”, the results showed a large use of wide spectrum antibiotics, for more days and a prolongation of mechanical ventilation and ICU stay [59]. To optimize the diagnostic accuracy and patient safety when PCT is used to guide the diagnostic and therapeutic decisions in patients with infections, two major points should be taken in consideration: the sensitivity of the used method and the normal reference values [6,55,56]. All the published studies on the administration of antibiotics used similar clinical algorithms with recommendations pro and against antibiotic use based on reference values of PCT. The reference values of PCT are extracted from the calculation of the multilevel-likelihood ratio from observational studies and reflect the odds of a bacterial infection. The feasibility and safety

of these algorithms were investigated in prospective ways and were proved repetitively from different control groups. A fall of the level of PCT up to ≤ 0,1 ng/mL is used to understand the end of bacterial invasion and that it is safe to interrupt antibiotic therapy [7,15,28,42,45,46]. Some studies have approved this approach as a better possibility than an arbitrary protocol with a precise duration of therapy. Almost every study up to now has showed a minimization in the duration of antibacterial therapy in the patients with sepsis or pneumonia, when guided based on consecutive measurements of PCT levels. The latest publications of Surviving Sepsis Campaign (SSC), 2016, show the importance of biomarkers (especially PCT) to support the shorter duration of antimicrobial therapy in patients with sepsis and the interruption of empirical antibiotics in patients that are considered to have sepsis at hospitalization, but who afterwards have resulted with clinical signs of infection [60]. Moreover, the real value of the biomarkers in decreasing the time of exposure to antibiotics should be evaluated in comparison to better available data and not in a strategy of prolongation of standard care (more than 7-8 days). Although PCT is the most studied biomarker related to the use of antibiotics, the combination of information from some biomarkers in clinical algorithms (52) can be useful and valuable for the patient [55]. All the studies published over the administration of antibiotics used similar clinical algorithms with recommendation pro and against the use with antibiotics based on reference values of PCT.

8. Other Potential used of Procalcitonin

The levels of PCT can help in the identification of the etiology of fever in patients with fever of unknown origin (FUO), because they do not increase in some diseases that cause FUO (for example, Still's disease, systemic lupus erythematous and inflammatory bowel disease). Some investigators have suggested that serum PCT is an appropriate tool to differentiate bacterial infections from SIRS (caused by viruses) or noninfectious diseases like trauma, burns and organ dysfunction [61]. The studies support the use of PCT in the diagnosis of pneumonia in emergency room [30, 62-64]. The data show that the levels of PCT are not influenced by the use of nonsteroid anti-inflammatory agents or glucocorticoids by the patients. The values of PCT lower than 0.5 are very useful for the early discharge of the patients from the hospital (in the fifth day after surgery) because it has a high predictive value. In a subgroup of 53 patients, PCT was measured up to the fifth day after surgery [41]. Daily measurement of PCT should be recommended in the first 3 days after abdominal surgery, always correlating the clinical, microbiologic and imaging evaluation. This algorithm is useful for the diagnosis of early potentially deadly infectious postoperative complications, like sepsis; for the early and appropriate use of antibiotics; for the early beginning of oral therapy; the appropriate indicator for CT exam; the number of days a patient stays in the hospital and to lower the cost of medical service [41]. It is important that, the levels of PCT should always be evaluated in the context of a careful clinical and microbiologic evaluation. Since the values of PCT have had a special

diagnostic and prognostic interest, repeated measurements should be done if it is possible, in patients who are continuously ill and are under antibiotic therapy [49].

9. Limitations of Procalcitonin

There is a number of limitations when using PCT as a marker of insfection and sepsis. Nonspecific increase of PCT levels, in absence of a bacterial infection, can result in situations of major stress, like after severe traumas and surgery, or in patients with cardiogenic shock [65]. This is the reason why PCT is better for the physicians than for the surgical patients in the differentiation of sepsis from a simple inflammation. Also, other cases of nonbacterial systemic inflammation are reported, including neonatal stress after birth, heat stroke and acute graft-vs-host disease, and other types of immunotherapy, like: granulocyte transfusion, the administration of antilymphocytic globuline or anti-CD3, and therapies with cytokines or bounded antibodies (IL-2 or TNF-α). Some autoimmune diseases like Kawasaki or different vasculitis and paraneoplastic syndromes, are also related with high values of PCT. The use of PCT measurements to manage patients with blood stream infections (BSIs) happens rarely for the elderly. It is not still clear how the patient's age can affect the levels of PCT in serum during BSIs. In a recent study from Stucker et al., the authors concluded that PCT in serum should not be considered as a reliable marker of BSI in elderly patients [61, 66]. PCT cannot be better than CRP in the diagnosis of bacterial infections in older patients, but its high specificity is useful to rule out bacterial infections [67]. In patients with hypothermia after a cardiac arrest, high initial levels of PCT were detected, but were not related to an infection. This increase in PCT was not specific and reflected an inflammatory reaction more than a real infection, thus, limiting the diagnostic potential of PCT and the early administration of antibiotics in these patients with high risk [27,38,68]. The limitations of every measurement of PCT include the falls-positive and falls-negative results [30]. Another limitation is related to the levels of PCT in serum which cannot be measured from many of hospital laboratories and to the fact that PCT is an expensive marker.

10. References

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