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Clinical Benefits of Procalcitonin

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INTRODUCTION

Microbes like bacteria or fungi can cause severe diseases in humans. Bacterial infection may proceed from superficial colonisation to local invasive infection and result in further systemic manifestations like sepsis. Mortality rates rise with increasing severity of inflammation. The most severe case of infection, complicated by systemic inflammation is severe sepsis and septic shock. The prevalence of sepsis, severe sepsis or septic shock in various countries is around 100 per 100,000.

In Germany, for example, with a population of 82 million, there are 160,000 patients with sepsis per year.

Since the disease may progress rapidly from a local process to systemic manifestations and organ dysfunction, time until diagnosis is a major issue in these patients(1).

Presently, there are a variety of options to effectively treat local infection and to prevent systemic spread and development of organ dysfunction such as antibiotic therapy, focus removal and specific approaches, as addressed by the SCCM surviving sepsis campaign (2).

However, to vigorously start such therapeutic efforts, an early reliable diagnosis is necessary and such therapy may be cost consuming or invasive (e.g. broad spectrum antibiotic treatment, surgical focus removal, intensive care treatment, supportive therapy like recombinant human activated protein C).

Clinical signs of sepsis and most biomarkers of inflammation indicate neither severity of inflammation nor probability of an infectious etiology of symptoms like SIRS. Modern markers like procalcitonin (PCT), however, are better able to indicate the course and severity of infection-induced inflammatory disease like septic shock.

The German Sepsis Society also emphasizes that an early and reliable diagnosis is very important for healing. In previous years some parameters were used in the clinical routine such as C-reactive protein or interleukins. However, they are unspecific inflammation parameters and not sensitive for bacterial infection. The newest parameter is procalcitonin (PCT, ProCT). It is very helpful in detection and assessment of the course of infection. The correct discrimination of clinical symptoms due to infection from those of inflammation has a direct influence on therapeutic decisions.

Use of a diagnostic parameter for bacterial infections like PCT provides a reliable estimation and decision in clinical practice:

1. Early diagnosis of severe invasive bacterial infections

2. Evaluation of the severity and prognosis of sepsis
3. Support of therapeutic decisions, both initially and during the course of disease
4. It should be a bio-stable marker, cost-effective and easy to determinate.

NATURE OF PROCALCITONIN

Procalcitonin is the prohormone of calcitonin. It consists of about 116 amino-acids (Figure 1). The locus of formation in classical pathway is the C-cells of the thyroid. Calcitonin has an influence on bone metabolism (3).

In case of bacterial infection, procalcitonin is formed in all tissues via an alternative pathway. Procalcitonin is not processed but will be secreted directly into the blood stream. This is why in septic patients extremely high concentrations of PCT were found in the plasma (about 100,000 fold of the physiological concentration in healthy subjects).

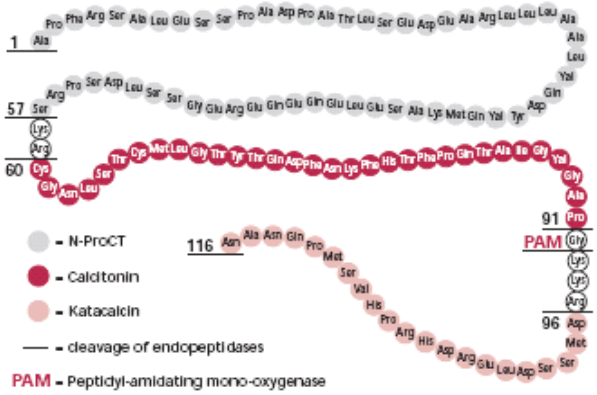


Figure 1. Structure of Procalcitonin.

Procalcitonin was investigated in about 500 trials as a clinical parameter in patients with different diseases.

In 2001, Harbarth et al (4). performed a prospective trial on 78 patients with suspected infection. PCT discriminated between patients with SIRS and sepsis and also between the degrees of severity of sepsis (Figure 2).

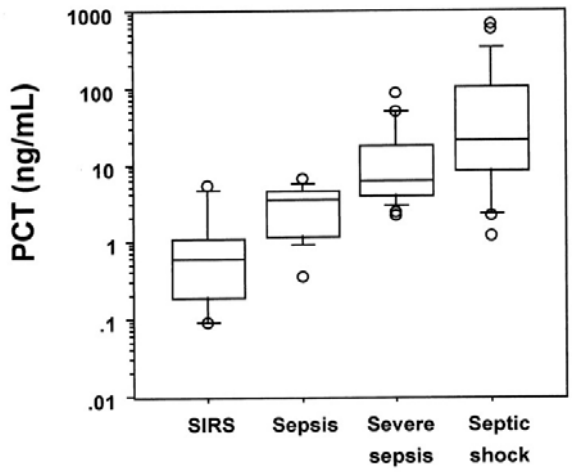


Figure 2. Correlation between the severity of disease and level of PCT-values

In the same study, Harbarth compared his clinical model with and without PCT. Procalcitonin enhanced the therapeutic safety of the treated physicians (Figure 3).

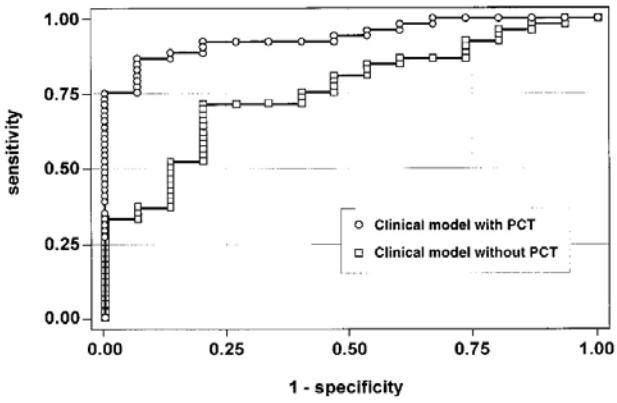


Figure 3. Increasing of the clinical diagnosis using PCT.

The choice of therapy is directed to the elimination of the infection source. Gendrel et al. (5) in 1999 investigated patients with meningitis. In this trial, they demonstrated that PCT had the potential to discriminate the source of meningitis to be either bacteria or virus. Only PCT can indicate bacterial meningitis. If the source is viral PCT values are very low. Only meningitis with a bacterial etiology can be

treated with antibiotics. So PCT will support therapy with antibiotics.

In case of chronic inflammation such as autoimmune diseases, the clinical symptoms are nearly the same as in bacterial infection. But the therapeutic decisions are completely different. In 1997, Eberhard et al. (6) conducted a trial on patients with autoimmune diseases (vasculitis and SLE) with or without infection. PCT concentration differentiated between both study groups and identified infected patients (Figure 4).

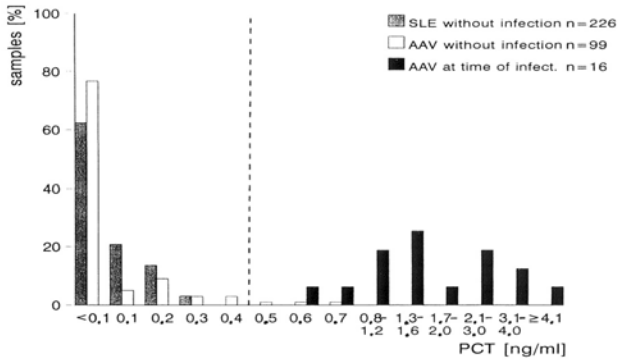


Figure 4. PCT- values in patients with autoimmune disease with or without infection.

Kuse et al. (7) and Pihusch et al. (8) demonstrated that PCT can discriminate infection or rejection in patients after transplantation. They also concluded that C-reactive protein and interleukins were not suitable for this purpose.

A formidable complication of mechanical ventilation of patients was ventilator-associated pneumonia. It leads to higher morbidity, mortality and higher costs. A new principle of monitoring of these patients provides the utilization of procalcitonin as a prognostic marker of therapeutic failure.

Luyt et al. (9) utilized PCT for detection of therapeutic failure and also for the prognostic evaluation of patients.

Patients with a PCT value > 0.5 ng/ml after 7 days of mechanical ventilation have a 64-fold risk of death, ongoing infection or relapse (Figure 5).

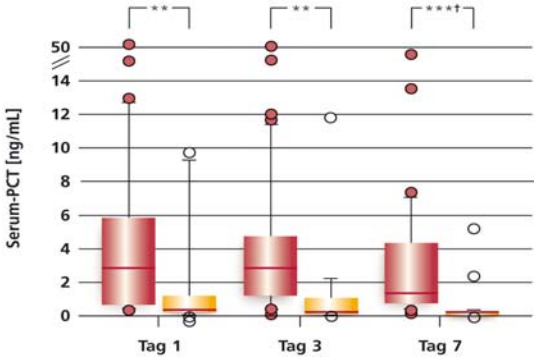


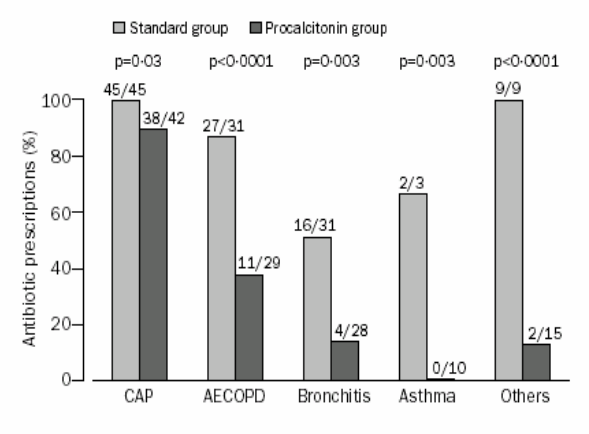
Figure 5. PCT concentration related to outcome
red column- non-survivor/ ongoing infection/ relapse
yellow column- survivor/ no infection

Procalcitonin as a tool to guide the antibiotic treatment in patients with infections of the lower respiratory tract

In 2004, Christ-Crain et al. (10) published data from an interventional study for the use of PCT to guide antibiotic treatment in patients with localized bacterial infections. They used a new highly-sensitive technique (Kryptor, BRAHMS Aktiengesellschaft, Hennigsdorf, Germany) to determine PCT in patients with lower respiratory tract infections. Two-hundred fourty-three patients were randomly divided into two groups. The control group received antibiotics according to the standardized practise. Patients in the procalcitonin group were treated with antibiotics according to a PCT- based algorithm:

< 0.1 ng/ ml: antibiotics strongly discouraged
< 0.25 ng/ ml: antibiotics discouraged
> 0.25 ng/ml: antibiotics encouraged
> 0.5 ng/ ml: antibiotics strongly encouraged

The procalcitonin group had a significant reduction in use of antibiotics and costs of about 50% (Figure 6).



CAP: community-aquired pneumonia; AECOPD: acute exacerbation of COPD

Figure 6. PCT-guided antibiotic prescriptions in patients with lower respiratory tract infection in comparison to the standard procedure

In 2006, the same authors created a new study. In a randomized interventional trial, 302 patients with suspected community-acquired pneumonia were consecutively entered in the study. The control group (151) received antibiotics according to the clinical practice. In the procalcitonin group (151) antibiotic therapy was guided according to the above mentioned algorithm.

The duration of antibiotic treatment could be diminished from 13 days to 5 days without deterioration of the outcome (11,12) (Figure 7).

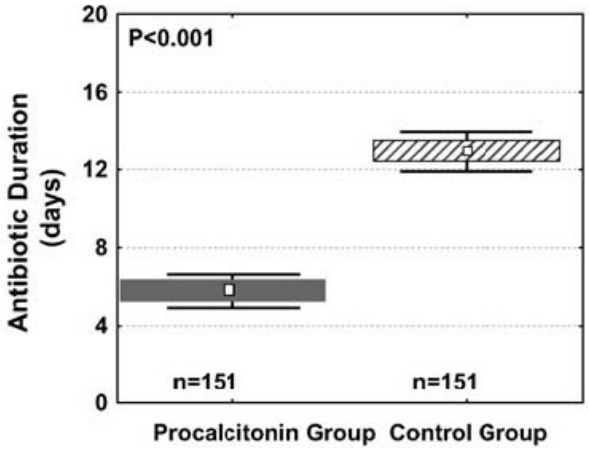


Figure 7. Duration of antibiotic treatment in procalcitonin and control group.

Other studies in patients with respiratory tract infections are ongoing to prove the impact of PCT on guided antibiotic use.

METHODS OF MEASUREMENT OF PCT

Currently, there are semi-quantitative quick-test and 4 quantitative immune assays available for the determination of procalcitonin. PCT can be measured in serum or plasma. Depending on the methods the results of determination are available after 19 min. to 2.5 hours (Figure 8).

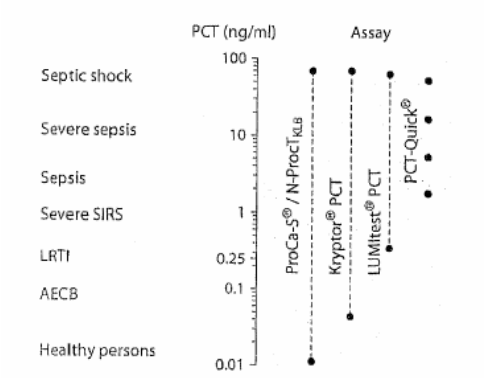


Figure 8. Use of available PCT- assays depends on clinical practice

Based on these scientific and clinical data the German Sepsis Society and the German Interdisciplinary Society of Intensive Care and Emergency Medicine have included PCT as the only diagnostic parameter in the guidelines for diagnosis and therapy of sepsis (13).

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