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## Procalcitonin – A New Indicator of the Systemic Response to Severe Infections

### Introduction

Severe infection and sepsis with consecutive multiple organ dysfunction or failure (MODS) are major causes of morbidity and mortality in modern intensive care units [1]. Recent advances in our understanding of the pathogenesis of sepsis have made it clear that uncontrolled infections, whether clinically manifest or occult, are not the only cause of systemic inflammation and organ dysfunction. Other stimuli such as pancreatitis [2], major trauma [3], and burns [4] can also trigger an excessive inflammatory response and lead to MODS. As a result, it is now generally accepted that not all patients displaying the clinical signs of sepsis have an underlying infection. It is therefore frequently difficult to distinguish patients with systemic infection from those who appear septic but have no bacteriological or clinical evidence of infection.

Common signs of systemic inflammation such as changes in body temperature, leukocytosis, and tachycardia may have an infectious or noninfectious etiology and are neither specific nor sensitive for sepsis. Thus, of 61 patients with sepsis (documented infection and at least two signs of remote organ failure), 35 (57%) presented with leukocytosis, 18 (29%) had leukopenia, and eight (14%) had normal leukocyte counts (unpublished data). Likewise, patients with sepsis may present with fever, hypothermia, or normal body temperature.

Bacteriological evidence of infection, although considered a gold standard, may have some drawbacks. Negative blood cultures do not exclude sepsis and multiple samples may be required over extended periods before positive cultures emerge [5]. Furthermore, positive or negative cultures may not develop concurrently with clinical signs of sepsis.

Because these common clinical and laboratory parameters lack sensitivity and specificity, others are needed to provide an early marker of the infectious etiology of a generalized inflammatory response and thus allow early diagnosis and the application of more specific therapeutic interventions. Furthermore, new parameters also may help identify subgroups of septic patients who may benefit from pro- or anti-inflammatory therapies. One such parameter, procalcitonin, has recently attracted attention as a possible marker of the systemic inflammatory response to infection.

### Physiology of Procalcitonin

Procalcitonin, a glycoprotein, is the propeptide of calcitonin devoid of hormonal activity. It consists of 116 amino acids with a molecular weight of 13 kD [6, 7], and under

normal circumstances, is produced in the C-cells of the thyroid gland. Procalcitonin is then cleaved via a specific protease to calcitonin, katacalcine, and an N-terminal residue [6]. In contrast to the short half-life of calcitonin (10 min), procalcitonin has a long half-life of 25–30 h [8] in serum. In healthy humans procalcitonin levels are undetectable (<0.1 ng/ml). During severe infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise to over 100 ng/ml, produced mostly by extra-thyroid tissues. Thus, patients who have previously undergone a total thyroidectomy can still produce high levels of procalcitonin during a severe infectious episode [9]. The exact site of procalcitonin production during sepsis is uncertain; one investigator, using katacalcine antibodies, has identified procalcitonin-like activity in human leukocytes [10], others suggest neuroendocrine cells and the lungs [11–13] as possible sites of production. Remarkably, the large amounts of procalcitonin produced during infections do not lead to an increase in plasma calcitonin levels or activity [9].

### Measurement of Procalcitonin

Previously, increases in serum calcitonin-like reactivities were found in patients with infections [14] or with lung disease [11, 12]. However, the methods employed did not discriminate between calcitonin and procalcitonin although some of the “calcitonin-like activity” in these studies may well be attributable to increases in procalcitonin levels. Today, procalcitonin is measured with an immunoluminometric assay (B.R.A.H.M.S. Diagnostika, Berlin). This assay is specific and uses two antibodies that bind to two sites (calcitonin and katacalcine) of the procalcitonin molecule, thus ruling out cross-reactivity. The detection limit of the assay is 0.1 ng/ml and procalcitonin levels of healthy subjects are usually < 0.1 ng/ml [15].

### Procalcitonin and Infectious Disease

Severe generalized bacterial, parasitic or fungal infections with systemic manifestation are associated with increased procalcitonin serum levels. In contrast, severe viral infections or inflammatory reactions of noninfectious origin do not, or only moderately increase procalcitonin levels. In

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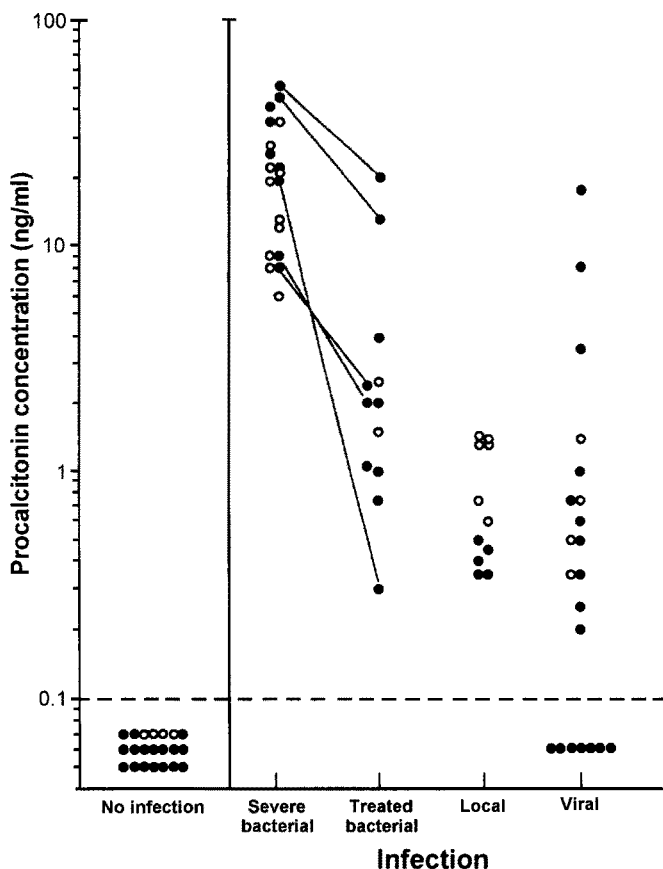


Figure 1: Serum procalcitonin concentrations in newborn infants (open circles) and older infants and children (filled-in circles). Reprinted with permission [9].

one well-conducted prospective study [9], 79 children with suspected infections displayed procalcitonin levels which were either very low ( $< 0.1$  ng/ml) in those with no infection, or very high (6–53 ng/ml) in those with severe infections. Antibiotic therapy in those with severe infections led to a resolution of the infection and to decreases in procalcitonin levels. Localized bacterial infections without systemic manifestations and viral infections produced only small to modest increases (0.3–1.5 ng/ml) (Figure 1). Calcitonin was undetectable in these patients regardless of how high procalcitonin levels were. In the same study, patients suffering from burns without (severe) infections had only modest elevations in procalcitonin levels, whereas those with severe infections had markedly elevated procalcitonin levels, suggesting that levels are increased during severe systemic bacterial infections, but not during viral infections or severe inflammatory reactions of noninfectious origin [9]. Because of these properties, procalcitonin has been proposed as a new parameter or indicator of severe generalized infections or sepsis [9, 15].

#### Procalcitonin and Cytokines

Cytokines have been implicated in the pathogenesis of severe infections and sepsis. Like procalcitonin, cytokines

such as tumor necrosis factor (TNF), IL-1 and IL-6 are frequently elevated in patients with severe bacterial infections (sepsis) [16, 17]. Healthy volunteers [18] injected with *Escherichia coli* endotoxin developed symptoms of systemic manifestation such as fever, myalgia, and chills 1–3 h later. Procalcitonin levels, undetectable at baseline, started to rise 4 h after endotoxin administration and plateaued at 4 ng/ml at 8–24 h. TNF and IL-6 levels peaked 2–3 h after endotoxin and were undetectable at 24 h (Figure 2). That the same kinetics can be expected to occur in human septic shock has been recently described in a rare and interesting case [19]. A hemodialysate of calf blood contaminated with *Acinetobacter baumannii* was injected into a 76-year-old patient leading, within hours, to septic shock. TNF was detectable in serum at 1.5 h, peaked at 3 h, and declined thereafter. Procalcitonin first detectable at 3 h, peaked 14 h after the injection at more than 300 ng/ml, and remained increased for more than 24 h. Thus, in response to endotoxin or to live bacteria, increases in circulating procalcitonin levels occur shortly after cytokines have peaked. Differences in the half-lives of procalcitonin (25–30 h) and the cytokines measured may explain why procalcitonin is detectable longer, or cytokines released after endotoxin administration might induce procalcitonin production. Unpublished observations (personal communication, Dr. Beier, Berlin) show that in cancer patients IL-2 or OKT3 infusions, or perfusion of isolated extremities with TNF lead to increases in procalcitonin levels. These reports, if substantiated, could better explain the described kinetics of procalcitonin and cytokines. Either way, although the chances of detecting elevated cytokine levels during severe infections are limited by their short half-lives, procalcitonin remains detectable in blood much longer. In a study at our institution [20], when compared to TNF and IL-6, procalcitonin best discriminated the severity of the inflammatory infectious response (Table 1). Furthermore, both TNF and IL-6 may decline despite persistence or even increased severity of sepsis, but procalcitonin levels remain elevated or may increase. The same cytokines are also frequently elevated in patients with (inflammatory) autoimmune disease (rheumatoid arthritis, lupus erythematosus), in which procalcitonin remains undetectable [8].

Increases in cytokine levels are not confined to the intravascular space and during infections, cytokine levels in body compartments (pleural fluid, bronchoalveolar fluid, cerebrospinal fluid, ascites) often exceed cytokine levels in intravascular space. In contrast, increased procalcitonin levels are mainly confined to the intravascular space and procalcitonin is either undetectable or markedly low in other body compartments [21].

#### Procalcitonin as an Indicator of the Inflammatory Response to Infectious Diseases

It is important to determine whether procalcitonin is a marker of (bacterial, fungal, or parasitic) infection, of the

Table 1: Procalcitonin, TNF- $\alpha$ , and IL-6 values in various stages of the inflammatory/infectious response.

	TNF- $\alpha$ (pg/ml)	IL-6 (pg/ml)	Proct (ng/ml)
SIRS	24 $\pm$ 4	269 $\pm$ 22	1.3 $\pm$ 0.2
Sepsis	51 $\pm$ 9*	435 $\pm$ 52*	2.0 $\pm$ 0.0*
Severe Sepsis	59 $\pm$ 17	969 $\pm$ 168*	8.7 $\pm$ 2.5*
Septic shock	118 $\pm$ 18	996 $\pm$ 57	38.6 $\pm$ 5.9*

Values are expressed in means  $\pm$  SEM. TNF- $\alpha$  = tumor necrosis factor alpha, IL-6 = interleukin-6, Proct = procalcitonin. SIRS = systemic inflammatory response syndrome. \*  $p < 0.05$  as compared to preceding value [20].

inflammatory response (to infectious or noninfectious stimuli), or only a marker of any severe degree of systemic host response (i.e. shock). Although many studies have been published on procalcitonin, as yet no study has provided satisfactory answers to these important questions. Clearly, procalcitonin is not a marker of infection as such since localized infections or infections with no systemic manifestation may not cause any appreciable increase in procalcitonin levels [22]. Procalcitonin levels increase only during infections with systemic manifestation. During such infections, the specificity of procalcitonin for infections increases with increasing procalcitonin values, i.e. patients with procalcitonin values above 1.5 ng/ml are more likely to have a severe infection (sensitivity 1.00, specificity 0.72) than patients with procalcitonin values between 0.1 and 1.5 ng/ml (sensitivity 1.00, specificity 0.35) [23]. However, the number of patients in such studies are limited and other investigations may report cut-off values above or below this level to obtain a certain level of diagnostic accuracy. Because of this, both high and low cut-off values of procalcitonin have been used to predict infectious complications in patients with an underlying active inflammatory disease. In patients with pancreatitis, pro-

calcitonin levels greater than 1.8 ng/ml predicted infectious complications with a diagnostic accuracy of 0.87, which was comparable to that of fine-needle aspiration (0.84) [24]. The diagnostic accuracy improved if increases in procalcitonin levels ( $> 1.8$  ng/ml) occurred at least twice during the observation period. In contrast, the cut-off value which was used to predict bacterial infection in patients with underlying active lupus erythematosus was merely 0.5 ng/ml [25], with a sensitivity of 1.00 and a specificity of 0.84. These findings suggest that levels of procalcitonin which best differentiate between infectious and noninfectious states in patients with underlying inflammatory syndrome may depend on the characteristics of the patient population studied.

Procalcitonin levels increase with increasing severity of the inflammatory response to infection. A recent study [23] compared procalcitonin values in patients with bacterial pneumonia and septic shock. Procalcitonin values were moderately increased in patients with bacterial pneumonia (mean: 2.4 ng/ml) but were markedly increased in patients with septic shock (means: 72–135 ng/ml). Preliminary results of other studies [20, 26, 27] suggest that once the procalcitonin level is increased, it then may reflect the severity of the inflammatory/infectious response. When patients were categorized into SIRS, sepsis, severe sepsis, and septic shock using ACCP/SCCM Consensus Conference Criteria [28], procalcitonin levels were especially elevated in patients with severe sepsis and septic shock (Table 1).

On the other hand, procalcitonin levels are not or only moderately increased in systemic inflammatory response to viral or to noninfectious stimuli (non-viral infections). In neonates and children, those with bacterial meningitis had significantly higher levels of procalcitonin (mean: 57.9 ng/ml) than those with viral meningitis (mean: 0.3 ng/ml) [29]. In patients infected with human immunodeficiency virus (HIV), procalcitonin levels were increased only in those with bacterial sepsis, whereas HIV infection alone, even in the last stages of disease, did not lead to increases in procalcitonin levels [30].

These findings have prompted investigators to use procalcitonin to differentiate between infectious and noninfectious causes of severe inflammatory states. Preliminary results suggest that procalcitonin helps differentiate an infectious (cholangitis by bile duct obstruction) from a non-

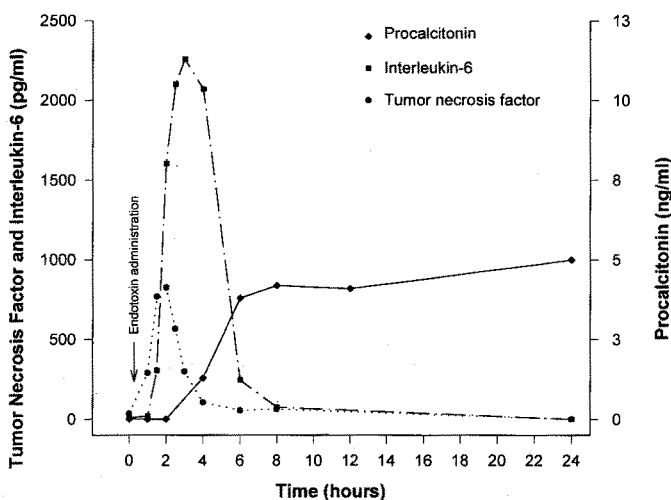


Figure 2: Serial procalcitonin (PCT), tumor necrosis factor (TNF- $\alpha$ ), and interleukin-6 (IL-6) values after endotoxin administration in humans. (Reprinted with permission [18] with modifications).

infectious (ethanol) etiology of pancreatitis [31], infectious from noninfectious causes of the acute respiratory distress syndrome in adults (ARDS), and systemic fungal [32] and bacterial infections from episodes of graft rejection [33] in patients after organ transplantation. These findings suggest that procalcitonin levels may help identify non-viral infection as a cause of the systemic inflammatory response.

Procalcitonin values in cardiogenic shock are only moderately increased (mean 1.4 ng/ml) in comparison to the large increases in patients with septic shock (means: 72–135 ng/ml) [23]. These findings show that increases in procalcitonin during septic shock are due to the inflammatory reaction to infection and not to poor organ perfusion. Thus, although the severity of the systemic response to infection is reflected in corresponding increases in procalcitonin levels, even severe disease of noninfectious etiology does not necessarily lead to corresponding increases in procalcitonin levels.

Since procalcitonin levels increase with increasing severity of the inflammatory response to infection they may be of prognostic value and may help evaluate therapeutic efficacy. In patients with melioidosis (infection with *Pseudomonas pseudomallei*), a fatal outcome was associated with significantly higher levels of procalcitonin than that seen in patients who survived [34]. In a study performed at our institution [35], procalcitonin values obtained on the day sepsis was diagnosed were significantly higher in non-survivors of sepsis as compared to survivors. Furthermore, procalcitonin levels increased during the course of disease in non-survivors whereas they decreased in surviving patients.

#### *Procalcitonin and C-Reactive Protein*

C-reactive protein is also a useful clinical tool in assessing the inflammatory response to infections. C-reactive protein has been successfully used to differentiate between true pneumonia and endotracheal infections in patients with chronic obstructive lung disease [36], to increase diagnostic accuracy in patients with appendicitis [37], to detect postoperative sepsis in infants [38], as an indicator of resolution of sepsis, and to differentiate between bacterial and viral infections [39]. In a recent study [40], C-reactive protein and procalcitonin were simultaneously measured in children with infectious disease. Procalcitonin increased earlier and returned to the normal range more quickly than C-reactive protein. Our clinical experience suggests that C-reactive protein may be an important marker in infections without systemic manifestation where procalcitonin concentrations are usually low. Procalcitonin, however, may be a superior marker during infections with systemic manifestation. Nevertheless, more studies are needed to determine whether procalcitonin is superior to C-reactive protein in differentiating between inflammation of infectious and noninfectious origin.

#### *Limitations of Procalcitonin as an Indicator of Infections*

It must be recognized that many studies concerning procalcitonin are observational studies in rather small patient populations or so far are reported only as short communications.

Procalcitonin may not or may only slightly increase when infection remains confined to a tissue or organ with no systemic manifestations. For example, with some exceptions, procalcitonin levels do not increase to more than a modest 1–2.4 ng/ml level during community-acquired pneumonia [22, 23]. In patients with localized infections without signs of systemic manifestation, therapeutic measures such as antibiotics or surgical intervention may be necessary despite normal procalcitonin levels. Although elevated procalcitonin values during severe infections may decrease to very low levels with appropriate therapy, this does not always indicate complete eradication of the infection but merely that generalization of the infection or the septic response is under control. Continuation of antibiotic therapy or surgical measures may be necessary until all clinical signs of infection have disappeared.

Procalcitonin levels may also occasionally be elevated in diseases with noninfectious causes. Patients with multiple trauma or after major surgery [41, 42], patients after cardiopulmonary bypass [43], and patients with C-cell carcinoma of the thyroid gland [44] and small-cell carcinoma of the lung [45] may present with increased procalcitonin levels without any evidence of severe infections. In high-risk cardiac surgery patients, procalcitonin was not helpful in differentiating between the inflammatory reaction to infection or to surgery as such [46]. However, in some cases procalcitonin levels decrease when no infectious complications occur, implying that changes in procalcitonin levels may be more informative than absolute values.

#### *Some Patient Groups in which Procalcitonin Measurement or Monitoring May Prove Useful*

Procalcitonin monitoring may be useful in patients likely to develop a systemic inflammatory response of infectious origin. Abrupt increases or high procalcitonin values in the following patient groups are indications for a search for a source of infection:

- Intensive-care unit patients after major surgery or trauma
- Intensive-care unit patients with nosocomial infections which may lead to sepsis
- Immunocompromised patients

Procalcitonin measurements may also be helpful in differentiating between infectious or noninfectious causes in patients presenting with a systemic inflammatory response syndrome:

- Pancreatitis (infectious-cholestatic versus alcohol-toxic and infected versus non-infected necrosis of the pancreas)
- Adult respiratory distress syndrome (infectious versus non-infectious)
- Transplantation patient (rejection reaction versus infections)

In addition, procalcitonin measurements may be helpful in differentiating between viral and bacterial infections (with systemic manifestation):

- Meningitis in neonates and children (viral versus bacterial)

### *Open Questions regarding the Nature and Use of Procalcitonin*

Despite the increasing number of studies, many questions regarding the nature and utility of procalcitonin still remain open:

- Which cells produce procalcitonin during infectious episodes?

- Which stimuli prompt these cells to produce procalcitonin?
- What purpose do high procalcitonin levels serve during severe infections?
- Large observational studies using adequate statistical means will be needed to determine when and whether procalcitonin is superior to conventional clinical and laboratory criteria in the differential diagnosis of severe inflammatory states.

Answers to these questions may lead to a more effective use of procalcitonin in predicting the presence and course of infections.

In conclusion, procalcitonin may prove to be a valuable indicator capable of identifying the presence and intensity of severe systemic non-viral infections.

### References

- Natanson, C., Hoffmann, W. D., Suffredini, A., Eichacker, P. Q., Danner, R. L.: Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Ann. Intern. Med.* 120 (1994) 771–783.
- Steinberg W, Tenner, S.: Acute pancreatitis. *N. Engl. J. Med.* 330 (1994) 1198–1205.
- Moore, F. A., Haanel, J. B., Moore, E. E., Whitehill, T. A.: Incomensurate oxygen consumption in response to maximal oxygen availability predicts postinjury multiple organ failure. *J. Trauma* 33 (1992) 58–67.
- Saffle, J. R., Sullivan, J. J., Tuohig, G. M., Larson, C. M.: Multiple organ failure in patients with thermal injury. *Crit. Care Med.* 21 (1993) 1673–1683.
- Gramm, H.-J., Reinhart, K., Goecke, J., Bülow, J. v.: Early clinical, laboratory, and hemodynamic indicators of sepsis and septic shock. In: *Reinhart, K., Eyrich, K.* (eds.): *Sepsis – an interdisciplinary challenge*. Springer-Verlag, Berlin 1989, pp. 45–57.
- Le Moullec, J. M., Jullienne, A., Chenais, J., Lasmoles, F., Guilana, J. M., Milhaud, G., Moukhtar, M. S.: The complete sequence of pre-procalcitonin. *FEBS* 167 (1984) 93–97.
- Jacobs, J. W., Lund, P. K., Potts, J. T., Bell, H. H., Habener, J. F.: Procalcitonin is a glycoprotein. *J. Biol. Chem.* 256 (1981) 2803–2807.
- Meisner, M.: PCT-procalcitonin. A new and innovative parameter in diagnosis of infections B.R.A.H.M.S. Diagnostica, Berlin 1996, pp. 14–60.
- Assicot, M., Gendrel, D., Carsin, H., Raymond, J., Guilbaud, J., Bohuon, C.: High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 341 (1993) 515–518.
- Oberhoffer, M., Vogelsang, H., Meier-Hellmann, A., Jäger, L., Reinhart, K.: Antikatacalcin-antibody reaction in different types of human leukocytes indicates procalcitonin content. *Shock* 7 (1997) 123 (abstr.).
- Nylen, E. S., Snider, R. H., Thompson, K. A., Rohatgi, P., Becker, K. L.: Pneumonitis-associated hypercalcitoninemia. *Am. J. Med. Sci.* 312 (1996) 12–18.
- Becker, K. L., O'Neill, W., Snider, R. H., Nylen, E. S., Jeng, J., Silva, O. L., Lewis, M. S., Jordan, M. H.: Hypercalcitoninemia in inhalation burn injury: a response of the pulmonary neuroendocrine cell? *Anat. Rec.* 236 (1993) 136–138.
- Cate, C. C., Pettingill, O. S., Sorensen, G. D.: Biosynthesis of procalcitonin in small cell carcinoma of the lung. *Cancer Res.* 46 (1986) 812–818.
- Mallet, E., Lanse, X., Devaux, A. M., Ensel, P., Basuyau, J. P., Brunelle, P.: Hypercalcitoninemia in fulminant meningococcaemia in children. *Lancet* i (1983) 294.
- Gendrel, D., Bohuon, C.: Procalcitonin, a marker of bacterial infection. *Infection* 25 (1997) 133–134.
- Leser, H.-G., Gross, V., Scheibenbogen, C., Heinisch, A., Salm, R., Lausen, M., Rückauer, K., Farthmann, E. H., Schölmerich, J.: Elevation of serum interleukin-6 concentration precedes acute phase response and reflects severity in acute pancreatitis. *Gastroenterology* 101 (1991) 782–785.
- Kragsbjer, P., Holmberg, H., Vikfors, T.: Serum concentrations of interleukin-6, tumor necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *Eur. J. Surg.* 161 (1995) 17–22.
- Dandona, P., Nix, D., Wilson, M. F., Aljada, A., Love, J., Assicot, M., Bohuon, C.: Procalcitonin increase after endotoxin injection in normal subjects. *J. Clin. Endocrinol. Metab.* 79 (1994) 1605–1608.
- Brunkhorst, F. M., Forycki, Z. F., Wagner, J.: Release and kinetics of procalcitonin (PCT) after gram-negative bacterial infection in a healthy subject. *Shock* 7 (1997) 124 (abstr.).
- Oberhoffer, M., Bigel, D., Meier-Hellmann, A., Vogelsang, H., Reinhart, K.: Procalcitonin vs immunological markers in infection/inflammation. *Br. J. Anaesth.* 76 (1996) A352 (abstr.).
- Brunkhorst, F. M., Forycki, Z. F., Wagner, J.: Identification of immuneactivation of infectious origin by procalcitonin-immunoreactivity in different body fluids. *Clin. Intensive Care* 7 (1996) 41 (abstr.).
- Gramm, H.-J., Dollinger, P., Beier, W.: Procalcitonin – a new marker of host inflammatory response. Longitudinal studies in patients with sepsis and peritonitis (translated from the German). *Chir. Gastroenterol.* 11 (Suppl. 2) (1995) 51–54.
- De Werra, I., Jaccard, C., Corradin, S. B., Chiolero, R., Yersin, B., Gallati, H., Assicot, M., Bohuon, C., Baumgartner, J.-D., Glauser, M. P., Heumann, D.: Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: Comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. *Crit. Care Med.* 25 (1997) 607–613.
- Rau, B., Steinbach, G., Gansauge, F., Mayer, J. M., Grünert, A., Beger, H. G.: The role of procalcitonin and interleukin-8 in the prediction of infected necrosis in acute pancreatitis. *Gut* (1997) (in press).
- Eberhard, O. K., Haubitz, M., Brunkhorst, F. M., Kliem, V., Koch, K. M., Brunkhorst, R.: Usefulness of procalcitonin for differentiation between activity of systemic autoimmune disease (systemic lupus erythematoses, systemic antineutrophil cytoplasmic antibody associated vasculitis) and invasive bacterial infection. *Arthritis Rheum.* 40 (1997) 1250–1256.
- Oberhoffer, M., Bitterlich, A., Hentschel, T., Meier-Hellmann, A., Vogelsang, H., Reinhart, K.: Procalcitonin (ProCt) correlates better with the ACCP/SCCM consensus conference definitions than other specific markers of the inflammatory response. *Clin. Intensive Care* 7 (1996) 46 (abstr.).
- Al-Nawas, B., Krammer, I., Shah, P. M.: Procalcitonin in the diagnosis of severe infections. *Eur. J. Med. Res.* 1 (1996) 331–333.

28. **Reith, H. B., Mittelkötter, U., Kamen, S., Beier, W., Dohle, J., Kozuschek, W.:** Procalcitonin – a parameter for the diagnosis of septic course? (translated from the German). *Langenb. Arch. Chir.* (1997) (in press).
29. **Gendrel, D., Raymond, J., Assicot, M., Moulin, F., Bergeret, M., Badoual, J., Bohuon, C.:** Procalcitonin in bacterial and viral meningitis in children. *Abstr. volume of ICAC, 20 September 1995* (1995) (abstr.).
30. **Gerard, Y., Hober, D., Assicot, M., Alfandari, S., Ajana, F., Bourez, J. M., Chidiac, C., Mouton, Y., Bohuon, C., Wattre, P.:** Procalcitonin as a marker of bacterial sepsis in patients infected with HIV 1. *J. Infect.* 35 (1997) 41–46.
31. **Brunkhorst, F. M., Forycki, Z. F., Wagner, J.:** Frühe Identifikation der biliären akuten Pankreatitis durch Procalcitonin-Immunität – vorläufige Ergebnisse (Early identification of acute biliary pancreatitis with procalcitonin immunoreactivity – preliminary results). *Chir. Gastroenterol.* 11 (1995) S47–S50 (abstr.).
32. **Gerard, Y., Hober, D., Petitjean, S., Assicot, M., Bohuon, C., Mouton, Y., Wattre, P.:** High serum procalcitonin level in a 4-year-old liver transplant recipient with a disseminated candidiasis (letter). *Infection* 23 (1995) 310–311.
33. **Stahler, M., Hammer, C., Meiser, B., Reichart, B.:** Procalcitonin: a new marker for differential diagnosis of acute rejection and bacterial infection in heart transplantation. *Transplant. Proc.* 29 (1997) 584–585.
34. **Smith, M. D., Suputtamongkol, Y., Chaowagul, W., Assicot, M., Bohuon, C., Petitjean, S., White, N. J.:** Elevated serum procalcitonin levels in patients with melioidosis. *Clin. Infect. Dis.* 20 (1995) 641–645.
35. **Oberhoffer, M., Bögel, D., Meier-Hellmann, A., Vogelsang, H., Reinhart, K.:** Procalcitonin is higher in non-survivors during course of sepsis, severe sepsis, and septic shock. *Intensive Care Med.* 22 (1996) A245 (abstr.).
36. **Smith, R. P., Lipworth, B. J.:** C-reactive protein in simple community acquired pneumonia. *Chest* 107 (1995) 1028–1031.
37. **Erikson, S., Grantström, L., Olander, B., Wretling, B.:** Sensitivity of interleukin-6 and C-reactive protein concentrations in the diagnosis of acute appendicitis. *Eur. J. Surg.* 161 (1995) 41–45.
38. **Chwals, W. J., Fernandez, M. E., Jamie, A. C., Charles, B. J., Rushing, J. T.:** Detection of postoperative sepsis in infants with the use of metabolic stress monitoring. *Arch. Surg.* 129 (1994) 437–442.
39. **Shaw, A. C.:** Serum C-reactive protein and neopterin concentrations in patients with viral or bacterial infection. *J. Clin. Pathol.* 44 (1991) 596–599.
40. **Monneret, G., Labaune, J. M., Isaac, C., Bienvenu, F., Putet, G., Bienvenu, J.:** Procalcitonin and C-reactive protein levels in neonatal infections. *Acta Paediatr.* 86 (1997) 209–212.
41. **Gramm, H.-J., Zimmermann, J., Quedra, N., Wegscheider, K.:** The procalcitonin (PROCT) response in severe sepsis is closely correlated to cytokine kinetics. *Shock* 7 (1997) A489 (abstr.).
42. **Marnitz, R., Gramm, H.-J., Zimmermann, J.:** Elaboration of mediators of inflammatory response after major surgery. *Shock* 7 (1997) 124 (abstr.).
43. **Meisner, M., Tschakowsky, K., Schmidt, J., Schüttler, J.:** Procalcitonin (PCT) – indications for a new diagnostic parameter of severe bacterial infection and sepsis in transplantation, immunosuppression, and cardiac assist devices. *Cardiovasc. Eng.* 1 (1996) 67–76.
44. **Bertagna, X. Y., Nicholson, W. E., Pettengill, O. S., Sorensen, G. D., Mount, C. D., Orth, D. N.:** Ectopic production of high molecular weight calcitonin and corticotropin by human small cell carcinoma cells in tissue culture: evidence for separate precursors. *J. Clin. Endocrinol. Metab.* 47 (1978) 1390–1393.
45. **Rau, F., Blind, E., Grauer, A.:** PDN-21 (katalcalin) and chromogranin A: tumor markers for medullary thyroid carcinoma. *Henry Ford Hosp. Med. J.* 40 (1992) 296–298.
46. **Pilz, G., Kreuzer, E., Appel, R., Werdan, K.:** Procalcitonin (PCT) serum levels in the early postoperative [period] of cardiac surgical patients at high risk for sepsis. *Shock* 7 (1997) 124 (abstr.).