

# Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections – hope for hype?

Philipp Schuetz<sup>a</sup>, Mirjam Christ-Crain<sup>a</sup>, Beat Müller<sup>a, b</sup>

<sup>a</sup> Department of Internal Medicine, University Hospital Basel, Basel, Switzerland

<sup>b</sup> Department of Internal Medicine, Kantonsspital Aarau, Aarau, Switzerland

## Summary

This review aims to provide physicians with an overview of the potential of procalcitonin to guide antibiotic therapy in respiratory tract infections and in sepsis. Knowledge of the strengths and weaknesses of procalcitonin are prerequisites for a rational and safe use in clinical routine. In most infections a true gold standard for diagnosis does not exist, therefore physicians must remain sceptical towards observational studies evaluating procalcitonin. Interpretation of procalcitonin levels must always include the clinical setting and knowledge of assay characteristics, particularly the setting of specific cut-off ranges and functional assay sensitivities. Highly sensitive procalcitonin measurements, embedded in a clearly defined setting and prospectively validated with clinical algorithms were repeatedly effective in markedly reducing the (over)-utilisation of antimicrobial therapy. Today, this concept has been proven for lower respiratory tract infections and in pilot studies for meningitis and critically ill patients with sepsis. The higher the absolute risk for adverse outcome of a patient, the more cautious physicians must remain and empirical antibiotic

therapies must be considered despite initial low procalcitonin levels at the initial presentation. In these patients a procalcitonin-guided shortening of antibiotic courses seems appropriate. The prognostic utility of initial procalcitonin measurement in respiratory tract infections is suboptimal. Other biomarkers including cortisol, human growth hormone and prohormones from adrenomedullin and vasopressin (“copeptin”) have a superior predictive potential to estimate the risk for short and long term mortality and other adverse outcomes in different diseases. An accurate prognostic assessment has the potential to optimise the management of patients and the allocation of our limited health care resources by lowering unnecessary hospitalisations and associated cost. Future intervention studies must prove if these biomarkers indeed improve clinical decision making and thus the overall medical management of patients.

*Key words: procalcitonin; prohormone; biomarker; prognosis; pneumonia*

## Biomarkers in sepsis

In bacterial sepsis, pathogens and their antigens stimulate a plethora of pro- and anti-inflammatory mediators which characterise the host defence and orchestrate leukocyte recruitment to the acute site of infection. Precursors, mature forms and degradation products of these different mediators penetrate from the initial site of action into the circulation, where, in theory, they can all be measured. As surrogate biomarkers these substances mirror the extent and severity of an infection. Enormous attempts have been undertaken to correlate the levels of different mediators with the presence of sepsis [1–3]. Procalcitonin (PCT) has been demonstrated to be clinically most use-

ful and superior to commonly used clinical variables and other laboratory tests in the diagnosis of sepsis and to correlate with the extent and severity of microbial invasion [2, 4–10]. The dual function of PCT as a precursor peptide from the hormone calcitonin and a cytokine mediator, which is elevated upon systemic bacterial infections in line with other cytokines, has led to the term “hormokine” mediator [11]. Other surrogate markers have been put forward to diagnose the presence of bacterial infections and guide antibiotic therapy. These include soluble triggering receptor expressed on myeloid cells-1 (s-TREM-1), [12, 13] C-reactive protein (CRP) [14] and white

PS, MCC and BM received support from BRAHMS to attend meetings and fulfilled speaking engagements. BM has served as a consultant and received research support.

blood cell count [15]. However, the usefulness of these markers for guiding antimicrobial therapy is not supported by controlled intervention trials and hampered by a delayed response with late peak levels, the need for invasive sampling of bronchoalveolar fluid (s-TREM-1) and their modulation by anti-inflammatory drugs such as corticosteroids, respectively [5, 16, 17]. Therefore, these tests have suboptimal practicability and diagnostic accuracy, especially in patients with systemic inflammation [13, 18–20].

Importantly, unlike other diagnostic biomarkers such as C-reactive protein (CRP), there is strong evidence from animal studies demonstrating that PCT plays a pathophysiological role in the development of severe sepsis and associated mortality. Administration of PCT to septic hamsters with peritonitis doubled their death rate [21]. Conversely, treatment with PCT-reactive antiserum increased survival of septic hamsters and pigs, with mono- and polymicrobial sepsis, respectively [21–24]. A one hour intravenous immuno-neutralisation of porcine PCT, improved all vital parameters in septic pigs. It increased short-term survival from 0% to 80% and was effective even when administered after the animals were moribund [22]. In humans, similar studies need to be funded.

As a diagnostic marker, PCT has several advantages over other inflammatory markers. The findings of many clinical studies have established

the superior diagnostic accuracy of PCT in severe infections [19, 25]. PCT shows an earlier increase upon infection and a more rapid decrease when the infection is controlled by the immune system supported by antibiotic therapy. PCT correlates with the extent and severity of infection and has prognostic implications, as the course of PCT predicts the risk for mortality in critically ill patients with infections [26] and in patients with ventilator-associated pneumonia (VAP) [16, 17, 26]. Furthermore, the production of PCT, in contrast to other biomarkers including CRP, seems not to be significantly attenuated by non-steroidal and steroidal anti-inflammatory drugs. [16, 17, 27] In this context it is interesting to note that the favourable effects of corticosteroids were reported in patients with pneumococcal pneumonia as early as 1955 [28]. More recently, a small prospective trial [29], and a large retrospective single centre trial suggested that the use of corticosteroids was associated with a lower mortality [30]. Other studies [31, 32] were not able to show a mortality benefit, however, a shorter duration of intravenous antibiotics and more rapid normalisation of inflammatory markers was found [32]. PCT concentrations were not assessed within these studies. Whether PCT is a useful biomarker for risk stratification and selection of those patients likely to profit from corticosteroids remains an open question

---

## The “gold standard” dilemma in sepsis

The presence of a diagnostic gold standard or reference standard remains the best available method for establishing the presence or absence of a disease [33, 34]. Optimally, a morphological verification such as histopathology or, in the case of sepsis, growth of typical pathogens in blood cultures can be obtained to establish the “correct” diagnosis. In this context, repeated collection of blood cultures to identify causative microorganisms and to study resistance patterns is propagated to be a cornerstone in the diagnostic work up of patients with suspicion of a sepsis syndrome. Regrettably, blood culture as the alleged “gold standard” lacks both sensitivity and/or specificity and is only available after a time delay. The causative microorganisms cannot be detected in up to 80% of patients with suspected BSI [8, 35]. Of note, in more than 70% of patients with radiologically confirmed community acquired pneumonia (CAP) the causative microbe is never identified. Conversely in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), typical respiratory bacterial strains are isolated from sputum in up to 50%, representing colonisation in many cases.

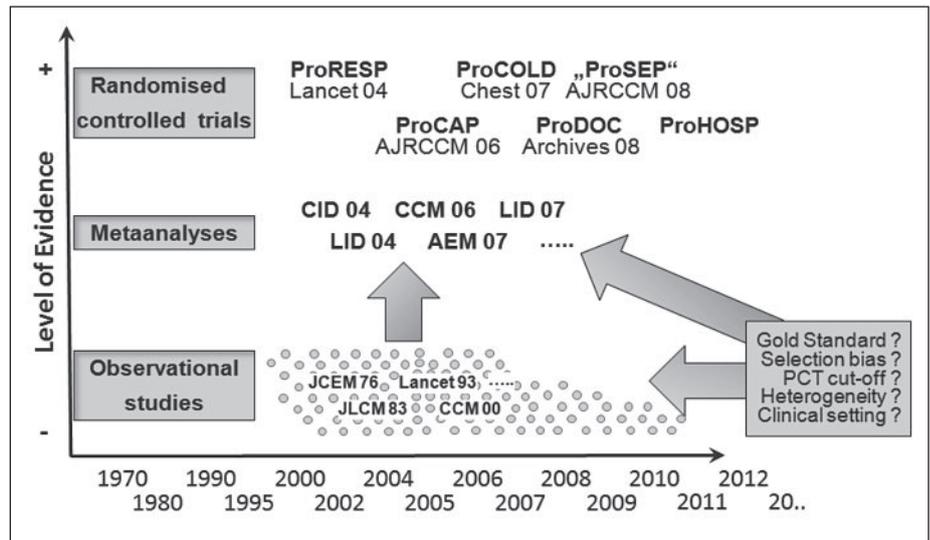
In this diagnostic uncertainty of bacterial infections, diagnostic surrogate biomarkers are of

interest. In the past years, countless observational studies have analysed a plethora of novel biomarkers and particularly PCT. In conventional diagnostic accuracy studies, the usefulness of a novel test is determined by comparing the results with the definite diagnosis ascertained by the gold standard. Sepsis is merely a clinical syndrome, not a final diagnosis, encompassing highly heterogeneous groups of disorders varying with respect to the site, bacteriology and even presence of infection, where a true gold standard is lacking [36]. In such circumstances, two fundamentally different concepts are used [34]. One concept tends to ignore potential dilemmas in the accuracy of the alleged “gold standard” but assumes a well-defined illness, which is represented by the assumption of a diagnostic test or a clinical diagnosis [34]. Many observational studies in different clinical settings using PCT assays have been published investigating the diagnostic accuracy of PCT for the diagnosis of sepsis (fig. 1). The majority of these studies used the clinical evaluation of the patient and the presence of the “septic syndrome” as the reference standard (“gold standard”). Accordingly, these observational studies and resulting meta-analyses [19, 25, 37–39] reported in part conflicting and confusing results since they are biased by

**Figure 1**

Potential drawbacks of observational studies in procalcitonin research. In recent years, a plethora of observational studies have investigated the diagnostic accuracy of PCT in different clinical settings. The majority of these observational studies used the clinical evaluation of the patient as the alleged "gold standard" to differentiate true bacterial infection or no infection. In addition, selection of patients, heterogeneity of clinical settings underlying diagnoses of patients and PCT assays with different functional assay sensitivities may lead to confounding study results. Unsurprisingly, these studies reported, at least in part, confusing and contradicting results. As a consequence, different metaanalyses drew different and even opposite conclusions depending on the inclusion of underlying studies. Only randomised controlled trials (RCTs), in which antimicrobial therapy is guided by PCT and in which the primary measure of efficacy is the medical outcome of patients, have the potential to resolve this dilemma and evaluate the clinical usefulness of PCT-guided antibiotic stewardship.

RCTs denote randomised controlled trials, observational studies [103–107], metaanalyses [19, 25, 37–39] and RCTs [45–51] are referenced. *AJRCCM* denotes American Journal of Respiratory and Critical Care Medicine; *Archives* denotes Archives of Internal Medicine; *CID* denotes Clinical Infectious Diseases; *CCM* denotes Critical Care Medicine; *LID* denotes Lancet Infectious Diseases, *AEM* denotes American journal of Emergency Medicine, *JCEM* denotes Journal of Clinical Endocrinology and Metabolism, *JLCM* denotes Journal of Laboratory and Clinical Medicine.



the interpretation of the investigator, and thus, should be interpreted with caution. The other concept discards alleged gold standards and focuses primarily on the outcomes of patients. In the case of sepsis, the clinical benefit of PCT can be measured by clinical outcomes of randomised intervention studies, assuming that if the patient recovers without antibiotics there was no relevant

bacterial illness. In our opinion, only randomised controlled trials (RCTs), in which antimicrobial therapy is guided by specific cut off ranges of PCT or other biomarkers and in which the primary measure of efficacy is medical outcome, have the potential to evaluate the ultimate clinical usefulness of a diagnostic biomarker.

## Procalcitonin for guidance of antibiotic therapy in respiratory tract infections

As PCT level increases upon bacterial infection and decreases upon recovery, it can be used to guide antibiotic therapy in individual patients as a surrogate biomarker. Highly sensitive PCT assays are needed to reliably diagnose CAP and non-CAP lower respiratory tract infection (LRTI) [40–43]. Using a highly sensitive PCT immunoassay with functional assay sensitivity of 0.06 µg/l, antibiotic stewardship based on PCT cut off ranges has successfully been implemented in patients with lower respiratory tract infections (LRTI) in different clinical settings [44–50]. For this purpose, specific PCT cut-off ranges, reflecting the setting specific likelihood of relevant bacterial infections, have been proposed and translated into a clinical algorithm (fig. 2). Based on these specific cut-off ranges, initiation or continuation of antibiotics was more or less discouraged (<0.1 µg/l or <0.25 µg/l) or encouraged (>0.5 µg/l or >0.25 µg/l), respectively. In case antibiotics were withheld, clinical re-evaluation and a repeated measurement of PCT was recommended after 6–24 hours. If PCT values were increased and antibiotic therapy was initiated, repeated PCT measurements were recommended and an-

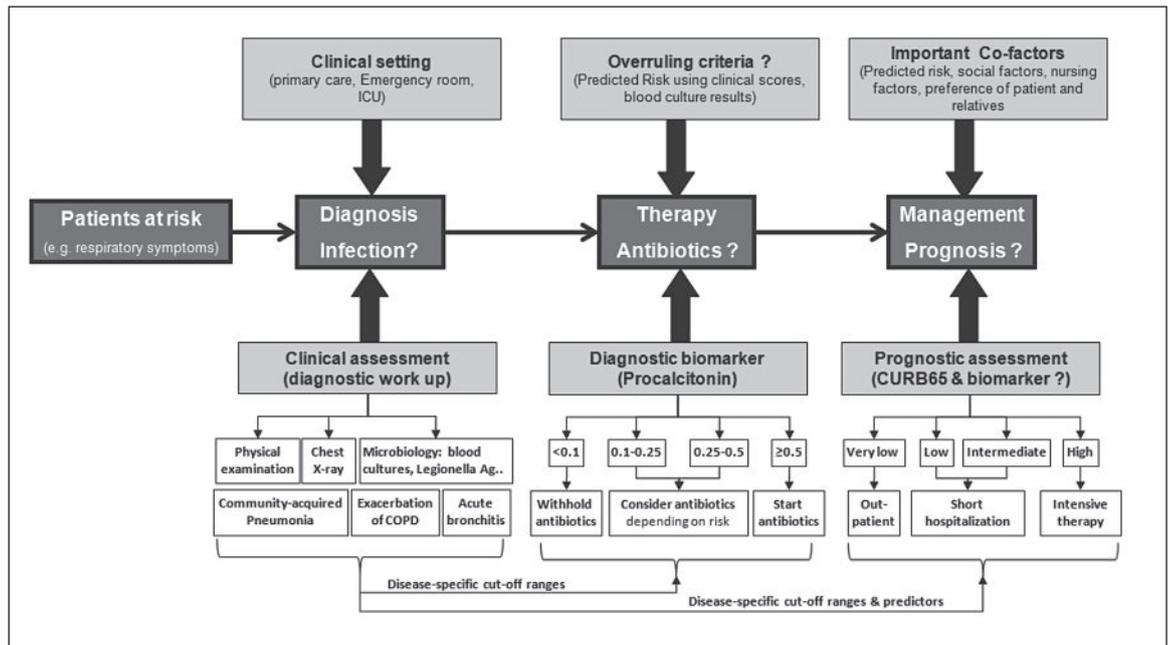
tibiotics were discontinued using the same cut-off ranges. In patients with very high PCT values on admission (e.g. >10 µg/l), discontinuation of antibiotic therapy was encouraged if levels decreased to below 80–90% of the initial value. To assure the safety of patients, specific "overruling" criteria were predefined, where this algorithm could be bypassed (e.g. life-threatening disease or immediate need for ICU admission). Physicians were advised that persistently elevated PCT levels may indicate a complicated course, while PCT levels may remain relatively low in localised infections (e.g. empyema or abscess). This clinical algorithm was prospectively tested in different intervention trials in the emergency room (ER) [45–48], in a pilot study in an intensive care unit (ICU) [51] and in a primary care setting with over 50 primary care physicians [49, 50]. Currently, this concept is being externally validated in the nationwide multi-centre ProHOSP study including over 1300 patients [46]. The validity of this algorithm was measured by good clinical outcomes. Thereby, PCT-guided antibiotic stewardship reduced the antibiotic prescription rate by 40–50% in patients with LRTI presenting to the emergency room, in-

**Figure 2**

Diagnostic and prognostic biomarkers for a better management of patients with lower respiratory tract infections.

Embedded in a pre-defined clinical algorithm, after history taking and a competent clinical examination, diagnostic and prognostic biomarkers improve the management of patients with respiratory tract infections (LRTI). In order to establish the correct diagnosis, clinical signs and symptoms including Chest X-ray and collection of blood cultures are most helpful. PCT as a diagnostic biomarker correlates with the likelihood of bacterial infection and PCT-guidance safely reduces antibiotic exposure in patients with LRTI and in critically ill septic patients. The further management of patients relies on different factors including social and nursing factors, preferences of patients and relatives and, importantly, on the predicted risk of patients. As different prognostic biomarkers (e.g. proADM, copeptin, proET-1) independently predict clinical outcomes of patients, namely mortality and need for ICU admission, these biomarkers have the potential to improve the management of patients and shorten unnecessary hospital stays.

LRTI denotes lower respiratory tract infection, ICU Intensive care unit.



cluding patients with acute exacerbation of chronic bronchitis (COPD), with no increase in relapse rate over a six month follow up period [48]. In patients with community-acquired pneumonia (CAP), PCT-guidance reduced the initial prescription rate by about 10%, but importantly shortened the duration of antibiotic therapy by 65% with a similar outcome in patients with all degrees of severity of CAP [47]. In the PARTI-study the safety and feasibility of the PCT guided algorithm was proven in primary care, with enrolment of more than 450 patients with acute upper and lower respiratory tract (RTI) [49, 50]. In a low antibiotic prescription setting in Switzerland, PCT-guidance safely reduced antibiotic exposure by more than 75% and thereby significantly re-

duced antibiotic-related side effects, especially diarrhoea. Using a similar PCT algorithm, a recently published trial including critically ill septic patients from a medical ICU reported a four day shorter duration of antibiotic therapy in PCT-guided patients (6 as compared to 10 days in the control group) with a similar mortality and recurrence rate [51]. Importantly, a two day shorter intensive care unit stay was observed in patients assigned to the PCT guided group. Large multicentre trials (ProHOSP [46], PRORATA, PASS) are currently being finalised as this review is in print. The cumulated evidence from RCT's will include almost 5000 patients, a truly remarkable number.

## Vascular catheter-related bloodstream infection

Commensals from the human skin flora, mainly coagulase-negative staphylococci, play a major role in catheter colonization. The distinction of blood contamination from blood stream infection (BSI) is important to promptly initiate an adequate therapy in true infection and, in case of contamination, to avoid unnecessary antimicrobial usage. Conventional methods of diagnosing catheter-related BSI generally require catheter removal and culture with quantitative or semi quantitative methods. However, the majority of catheters are withdrawn unnecessarily and the removal of a central venous catheter may be undesirable because of limited vascular access and the potential complications associated with reinsertion. Thus, diagnostically reliable and more cost-effective diagnostic approaches that do not re-

quire catheter removal would be desirable. In this context, the diagnostic value of serum PCT to distinguish blood contamination from BSI due to coagulase-negative staphylococci has been evaluated in a pilot study [10]. Therein, PCT demonstrated a better discriminatory ability as compared to white blood count and serum CRP. In this study [10] increased PCT concentrations were found even prior to the clinical manifestation of BSI (i.e. fever) illustrating the high sensitivity of PCT to detect colonization of the catheter with only sub-clinical infection ultimately leading to BSI [52]. Importantly, the optimal cut off to achieve a 100% sensitivity in this study was at a low PCT cut-off of 0.1  $\mu\text{g/l}$  illustrating, once again, the need for a highly sensitive PCT assay in many clinical settings outside the ICU [53].

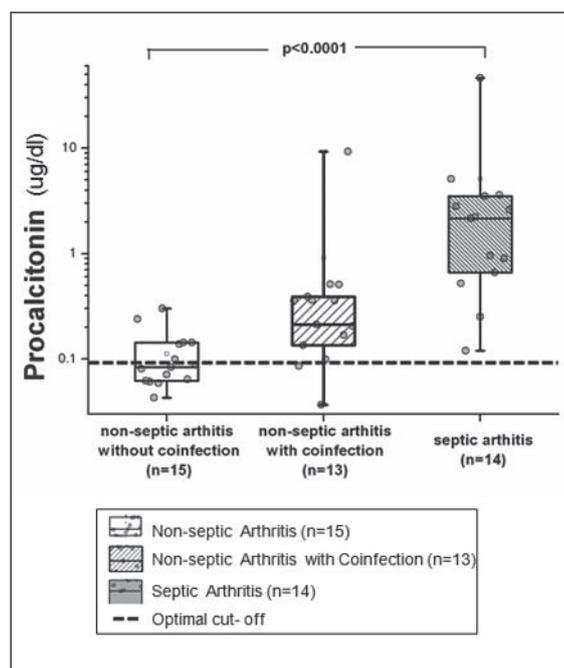
## Differentiation of septic from non-septic arthritis

**Figure 3**

Differentiation of septic and non-septic arthritis.

Early differentiation between septic and non-septic arthritis and the possible decision for early therapy remain a difficult task for the physician. In a pilot study including 42 patients with bacterial and non-bacterial arthritis, PCT was shown to be the most accurate diagnostic biomarker as compared to CRP and white blood cell count [108]. Importantly, using a highly sensitive PCT assay with a cut-off in the range of healthy persons (0.1 µg/l), sensitivity for septic arthritis was 100% and specificity 46%. The area under the receiver operating characteristic (ROC) curve (AUC) of PCT was 0.92 as compared to 0.72 of CRP.

*Non-septic arthritis with coinfection* refers to patients with systemic bacterial infections and concomitant diagnosis of gout arthritis.



Early differentiation between septic and non-septic arthritis is of utmost importance to prompt adequate initial therapy and surgical measures. As clinical signs and traditional markers of infection are of only limited value in ruling out a bacterial aetiology, arthrocentesis with synovial gram stain and culture is mandatory. Even so the sensitivity of gram staining is only 50–75% and culture is not available immediately [54]. A more specific diagnostic biomarker would thus be most useful. Previous studies evaluating PCT in this setting have been inconclusive, mainly because of small and heterogenic patient populations and because they used only semi quantitative PCT assays [55–58]. A recent study including 42 patients with septic and non septic arthritis found PCT to be most useful and superior to other markers of infection. Importantly, PCT had a sensitivity of 100% (93%) to rule out bacterial infection, when a low PCT cut off in the normal range of 0.1 µg/dl (0.25 µg/dl) was used (fig. 3).

## Biomarkers for prognostic assessment

LRTI and particularly CAP is the leading cause of sepsis and death from infectious diseases in western countries and health expenditures in particular for inpatient management are substantial [59, 60]. Accurate assessment of disease severity, risk stratification and prediction of outcome are prerequisites for safe decision making on the need for hospitalisation and identifying patients at low risk of complications and thus suitable for outpatient management. Despite their widespread use in clinical routine, traditional markers such as severity of disease estimation by the patient, fever, white blood cells and CRP do not reliably assess disease severity and mortality risk [2]. Several organizations have developed prediction rules and disseminated guidelines to stratify management of patients based on predicted mortalities in order to optimise hospital referral and lower hospital admission rates [61, 62]. The pneumonia severity index (PSI) is an extensively validated and widely propagated American scoring system that assesses the risk of death in a two step algorithm [63]. However, its complexity jeopardizes its dissemination and implementation in everyday practice. Therefore, the CURB-65 and the CRB-65 scores, modified versions of the British Thoracic Society (BTS) assessment tool, which are based on only five and four predictors, respectively, have been proposed as a simpler but somewhat less reliable alternative [64, 65]. All these scores, however, have only been evaluated in CAP and not in all LRTI, and for mortality and not other serious adverse events requiring hospitalisation. They are heavily age-dependent and have a considerable risk of

misclassification and thus misclassification of patients depending on the clinical setting [66]. In this context, new measurable biomarkers mirroring distinct pathogenetic mechanisms to predict severity and outcome may improve prognoses of patients. Importantly, the utility of a biomarker in this context is defined by the degree it improves clinical decision making and adds timely information beyond that of readily available information from clinical examination [67].

While a prognostic value of PCT in critically ill patients from the intensive care unit has repeatedly been demonstrated [68, 69], the prognostic value of a single level on admission is only suboptimal. A recent study suggested that very low PCT values on admission (optimal PCT cut off at 0.23 µg/l) in patients with community acquired pneumonia (CAP) have a moderate negative prognostic value and thereby improve the CRB65 score [70]. Similarly, in patients with CAP due to Legionella, high initial PCT concentrations predicted adverse outcome in patients including mortality and need for ICU admission (fig. 4) [71]. This being said, it is even more helpful to consider the dynamics of PCT levels in LRTI, as persistently elevated levels are associated with adverse outcome and decreasing PCT levels suggest a favourable outcome, usually showing a log-linear drop off and a half life of 20 to 24 hours [4, 70, 72]. Similarly in the ICU setting, elevated PCT levels, and especially a PCT increase for one day were independent predictors for 90-day all cause mortality in septic patients [26], while increasing levels of CRP and white blood cells did not pre-

dict mortality. Similarly in our studies, PCT showed a better prognostic accuracy compared to CRP and white blood cells, but there was a wide overlap in PCT levels between different severities of CAP and only a small difference in PCT levels between survivors and non-survivors [2, 5, 43, 73]. Based on these data, PCT seems to be a reliable diagnostic marker able to guide decisions on antibiotic therapy rather than an ideal prognostic tool. This is a disadvantage especially on admission where the costly decision for in- or outpatient treatment has to be made [2, 5, 73, 74].

A more promising prognostic biomarker on admission is adrenomedullin (ADM). It is also a member of the CALC gene family, and is very potent vasodilating agent with additional immune modulating and metabolic properties [75–78]. Measurement of ADM is challenging, since it is rapidly cleared from the circulation [75, 76]. A new sandwich immuno-assay, which measures the more stable mid regional fragment of pro-adrenomedullin (proADM) directly reflecting levels of the rapidly degraded active peptide, has been developed [79]. In patients with CAP, proADM levels measured on admission showed a comparable correlation with disease severity and outcome of CAP as compared to the PSI. Importantly, proADM improved the prognostic accuracy of the PSI alone, acting as an additional margin of safety [73].

During severe illness a series of other important hormonal changes happen mirroring the patients individual “stress level” [80–82]. For this reason, stress hormones *per se* are promising candidate “biomarkers” for the prognostic assessment of patients with systemic infections. The classical stress response of the body includes a stimulation of the hypothalamic-pituitary-adrenal axis with an increased production of cortisol and vasopressin levels and a functional deficit of anabolic hormones [80, 81]. As plasma cortisol levels mirror the individual stress level associated with the underlying illness, we evaluated the prognostic value of cortisol in patients with CAP [83]. Cortisol concentrations measured on presentation accurately predicted the severity and outcome of CAP at a level similar to the PSI and higher as compared to commonly measured laboratory parameters, namely CRP, white blood cells

and PCT. The higher level of pro-inflammatory cytokines in patients who subsequently died may additionally explain the pronounced increase of cortisol as the strongest known natural inhibitor of inflammation in non surviving patients.

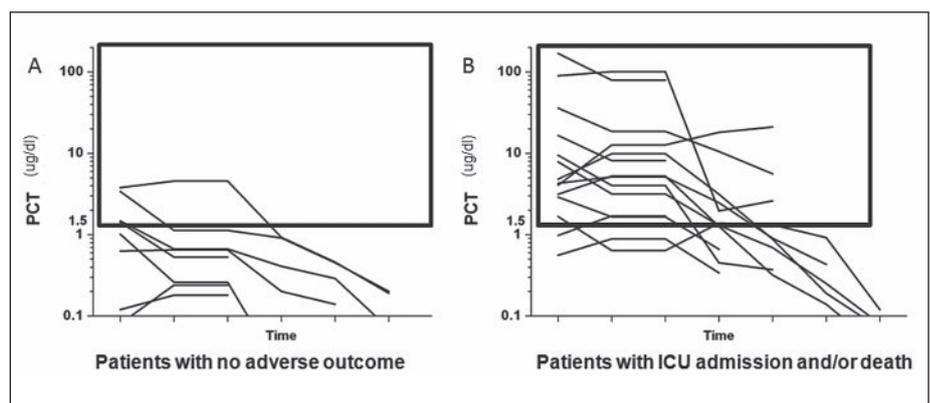
Circulating levels of growth hormone are increased during critical illness and correlate with outcome in children with meningococcal sepsis. Growth hormone plasma concentrations on admission are independent predictors for mortality in critically ill adult patients and may complement existing risk prediction scores, namely the APACHE II and the SAPS II score [84].

Another, less known but nevertheless pivotal stress hormone is the anti-diuretic hormone (ADH), also known as vasopressin, which has haemodynamic and osmoregulatory effects and reflects the individual stress response. This hormone co-regulates the secretion of ACTH together with corticotrophin releasing hormone. Copeptin which is stoichiometrically co-secreted with vasopressin, and directly mirrors vasopressin production, has a longer half life in the circulation and is thus easier to measure [85]. We evaluated the prognostic value of copeptin and found significantly higher concentrations in patients with LRTI as compared to controls with highest levels in patients with CAP [86]. Copeptin levels increased with increasing severity of CAP, and in patients who died, copeptin levels on admission were significantly higher as compared to levels in survivors [86]. Recently, in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) copeptin was shown to be predictive for long-term clinical failure, independent of age, comorbidity, hypoxaemia and lung functional impairment in multivariate analysis [87]. The combination of copeptin and previous hospitalisation for COPD increased the risk of poor outcome.

Another interesting endothelium derived biomarker is endothelin-1 (ET-1) and its precursor peptide proET-1 [88]. In humans, elevated plasma levels of mature ET-1 are found during systemic infections and correlate with mortality risk [89–91]. Preliminary studies in animals have demonstrated beneficial effects of ET-1 antagonism using a selective ET-1 receptor antagonist [9] during septic shock [92–95]. Using a new sandwich immunoassay, we recently evaluated proET-1 levels

**Figure 4**

PCT concentrations in CAP due to Legionella. A recent retrospective study including patients with CAP due to Legionella found that initial PCT concentrations and the course of PCT have prognostic implications: patients with initially high (optimal cut off >1.5 µg/dl) or increasing PCT concentration have a higher risk for death and/or need for ICU admission as compared to patients with low or decreasing PCT concentrations [71].



in patients with CAP and found proET-1 on admission to be independent predictors of short term mortality and need for ICU admission. In this setting, proET-1 levels improved the prognostic accuracy of the commonly used CURB65 score to predict adverse outcome [96]. Interestingly in critically ill and septic patients from a medical ICU, the ratio of the endothelium-derived and counter-acting substances proADM and proET-1 showed the highest predictive accuracy [97].

It is advisable to base the difficult task of prognostic assessment and treatment decisions on several rather than a single parameter. We have thus studied other hormonal and metabolic mediators and biomarkers in CAP and in LRTI, in-

cluding brain-natriuretic-peptide (BNP) [98], N-terminal pro-atrial natriuretic peptide (MR-proANP) levels [99, 100] and plasma lipid levels [101, 109], each mirroring different pathophysiological aspects, showing promising results in predicting disease severity and outcome [2, 102].

There is rational and emerging evidence that different biomarkers have the potential to complement existing clinical severity scores and thus improve the risk stratification of patients with LRTI. However, specific cut off ranges need to be proposed and prospective intervention studies conducted to order to decide if these biomarkers really do improve the daily clinical management of patients with sepsis.

## Limitations of biomarkers

Obviously, the septic syndrome is far too heterogeneous and complex to be reduced to a single cut-off of any one surrogate marker. Different microbes might induce distinct responses resulting in a variable upregulation of circulating biomarkers and mediators. Still, the likelihood of a bacterial infection increases gradually with increasing serum levels of PCT. Knowledge of assay characteristics, particularly the functional assay sensitivity and the strengths, pitfalls and optimal cut off ranges in a predefined clinical settings are prerequisites for its optimal use in clinical routine.

Importantly, biomarker levels must always be evaluated in the context of a careful clinical and microbiological assessment. As the kinetics of biomarkers are of particular diagnostic and prognostic interest, repeated measurements should always be performed, especially if antibiotics are withheld and in persistently sick patients. In addition, immuno-modulating drugs may suppress the upregulation of different biomarkers. While the kinetics of PCT are less influenced by corticosteroids, CRP, proADM, proANP and Copeptin are inhibited in a dose-dependent way upon prednisone treatment [27]. Limitations of every bio-

marker include false-positive and false-negative results [16]. Unspecific elevations of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive stress, e.g. after severe trauma or surgery [16, 25]. In these situations, PCT values are usually only moderately elevated and show a rapid decline in the follow up measurements. Conversely, falsely low PCT levels, typically seen during the early course or localised state of an infection, often show an increase in the follow-up measurements. Importantly, in these situations highly sensitive PCT assays are required, as subtle changes of PCT at very low concentration can be monitored increasing its sensitivity and thus the safety of patients.

### Correspondence:

Beat Mueller

Department of Internal Medicine

Kantonsspital

Tellstrasse

CH-5001 Aarau

Switzerland

happy.mueller@unibas.ch

## References

- Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. *J Infect Dis.* 2000; 181:176–80.
- Christ-Crain M, Muller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J.* 2007;30:556–73.
- Muller B, Schuetz P, Trampuz A. Circulating biomarkers as surrogates for bloodstream infections. *Int J Antimicrob Agents.* 2007;30(Suppl 1):S16–23.
- Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med.* 2001;164:396–402.
- Muller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis.* 2007;7:10.
- Morgenthaler NG, Struck J, Fischer-Schulz C, Seidel-Mueller E, Beier W, Bergmann A. Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. *Clin Lab.* 2002;48:263–70.
- Muller B, Becker KL. Procalcitonin: how a hormone became a marker and mediator of sepsis. *Swiss Med Wkly* 2001, 131:595–602.
- Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R: Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med.* 2000;28:977–83.
- Stolz D, Christ-Crain M, Gencay MM, Bingisser R, Huber PR, Muller B, Tamm M. Diagnostic value of signs, symptoms and laboratory values in lower respiratory tract infection. *Swiss Med Wkly.* 2006;136:434–40.
- Schuetz P, Mueller B, Trampuz A. Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. *Infection.* 2007;35:352–5.

- 11 Muller B, White JC, Nylen ES, Snider RH, Becker KL, Habener JF. Ubiquitous Expression of the Calcitonin-1 Gene in Multiple Tissues in Response to Sepsis. *J Clin Endocrinol Metab.* 2001;86:396-404.
- 12 Gibot S, Cravoisy A, Kolopp-Sarda MN, Bene MC, Faure G, Bollaert PE, Levy B. Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. *Crit Care Med.* 2005;33:792-6.
- 13 Muller B, Gencay MM, Gibot S, Stolz D, Hunziker L, Tamm M, Christ-Crain M. Circulating levels of soluble triggering receptor expressed on myeloid cells (sTREM)-1 in community-acquired pneumonia. *Crit Care Med.* 2007;35:990-1.
- 14 Smith RP, Lipworth BJ, Cree IA, Spiers EM, Winter JH. C-reactive protein. A clinical marker in community-acquired pneumonia. *Chest.* 1995;108:1288-91.
- 15 McCarthy PL, Tomasso L, Dolan TF Jr. Predicting fever response of children with pneumonia treated with antibiotics. *Clin Pediatr (Phila)* 1980;19:753-60.
- 16 Christ-Crain M, Muller B. Procalcitonin in bacterial infections – hype, hope, more or less? *Swiss Med Wkly.* 2005;135:451-60.
- 17 Muller B, Peri G, Doni A, Perruchoud AP, Landmann R, Pasqualini F, Mantovani A. High circulating levels of the IL-1 type II decoy receptor in critically ill patients with sepsis: association of high decoy receptor levels with glucocorticoid administration. *J Leukoc Biol.* 2002;72:643-9.
- 18 van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ.* 2005;331:26.
- 19 Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis.* 2004;39:206-17.
- 20 Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. *N Engl J Med.* 2004;350:451-8.
- 21 Nylen ES, Whang KT, Snider RH Jr, Steinwald PM, White JC, Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. *Crit Care Med.* 1998;26:1001-6.
- 22 Becker KL, Nylen ES, Snider RH, Muller B, White JC. Immunoneutralization of procalcitonin as therapy of sepsis. *J Endotoxin Res.* 2003;9:367-74.
- 23 Wagner KE, Martinez JM, Vath SD, Snider RH, Nylen ES, Becker KL, et al. Early immunoneutralization of calcitonin precursors attenuates the adverse physiologic response to sepsis in pigs. *Crit Care Med.* 2002;30:2313-21.
- 24 Martinez JM, Wagner KE, Snider RH, Nylen ES, Muller B, Sarani B, et al. Late immunoneutralization of procalcitonin arrests the progression of lethal porcine sepsis. *Surg Infect. (Larchmt)* 2001;2:193-202; discussion 202-3.
- 25 Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med.* 2006;34:1996-2003.
- 26 Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med.* 2006;34:2596-602.
- 27 de Kruif MD, Lemaire LC, Giebelen IA, Struck J, Morgenthaler NG, Papassotiropoulos J, et al. The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. *Intensiv Care Med.* 2008;34:518-22.
- 28 Wagner HN, Bennett IL, Lasagna L, Cluff LE, Rosenthal MB, Mirick GS. The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. *Bulletin of Johns Hopkins Hospital.* 1955;98:197-215.
- 29 Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med.* 2005;171:242-8.
- 30 Garcia-Vidal C, Calbo E, Pascual V, Ferrer C, Quintana S, Garau J. Effects of systemic steroids in patients with severe community-acquired pneumonia. *Eur Respir J.* 2007;30:951-6.
- 31 Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. *Chest.* 1993;104:389-92.
- 32 Mikami K, Suzuki M, Kitagawa H, Kawakami M, Hirota N, Yamaguchi H, et al. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. *Lung.* 2007;185:249-55.
- 33 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med.* 2003;138:W1-12.
- 34 Bachmann LM, Juni P, Reichenbach S, Ziswiler HR, Kessels AG, Vogelstein E. Consequences of different diagnostic “gold standards” in test accuracy research: Carpal Tunnel Syndrome as an example. *Int J Epidemiol.* 2005;34:953-5.
- 35 Pizzo PA. Evaluation of fever in the patient with cancer. *Eur J Cancer Clin Oncol.* 1989;25(Suppl 2):S9-16.
- 36 Marshall JC. Sepsis: rethinking the approach to clinical research. *J Leukoc Biol.* 2008;83:471-82.
- 37 Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials.* 2005;2:209-17.
- 38 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;7:210-7.
- 39 Jones AE, Fiechtel JF, Brown MD, Ballew JJ, Kline JA. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. *Ann Emerg Med.* 2007;50:34-41.
- 40 Boussekey N, Leroy O, Georges H, Devos P, d'Escurain T, Guery B. Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. *Infection.* 2005;33:257-63.
- 41 Polzin A, Pletz M, Erbes R, Raffenberg M, Mauch H, Wagner S, Arndt G, Lode H. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. *Eur Respir J.* 2003;21:939-43.
- 42 Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with aetiology and prognosis. *Infection.* 2000;28:68-73.
- 43 Masia M, Gutierrez F, Shum C, Padilla S, Navarro JC, Flores E, Hernandez I. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. *Chest.* 2005;128:2223-9.
- 44 Snider RH Jr, Nylen ES, Becker KL. Procalcitonin and its component peptides in systemic inflammation: immunochemical characterization. *J Investig Med.* 1997;45:552-60.
- 45 Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest.* 2007;131:9-19.
- 46 Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. *BMC Health Serv Res.* 2007;7:102.
- 47 Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med.* 2006;174:84-93.
- 48 Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Muller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet.* 2004;363:600-7.
- 49 Briel M, Christ-Crain M, Young J, Schuetz P, Huber P, Periat P, et al. Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]. *BMC Fam Pract.* 2005;6:34.
- 50 Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med.* 2008;168:2000-7; discussion 2007-8.
- 51 Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med.* 2008;177:498-505.
- 52 Catton JA, Dobbins BM, Kite P, Wood JM, Eastwood K, Sugden S, et al. In situ diagnosis of intravascular catheter-related bloodstream infection: a comparison of quantitative culture, differential time to positivity, and endoluminal brushing. *Crit Care Med.* 2005;33:787-91.
- 53 Nylen ES, Muller B, Becker KL, Snyder RH. The future diagnostic role of procalcitonin levels: the need for improved sensitivity. *Clin Infect Dis.* 2003;36:823-4.
- 54 Goldenberg DL. Septic arthritis. *Lancet.* 1998;351:197-202.
- 55 Soderquist B, Jones I, Fredlund H, Vikerfors T. Bacterial or crystal-associated arthritis? Discriminating ability of serum inflammatory markers. *Scand J Infect Dis.* 1998;30:591-6.
- 56 Butbul-Aviel Y, Koren A, Halevy R, Sakran W. Procalcitonin as a diagnostic aid in osteomyelitis and septic arthritis. *Pediatr Emerg Care.* 2005;21:828-32.
- 57 Martinot M, Sordet C, Soubrier M, Puechal X, Saraux A, Liote F, et al. Diagnostic value of serum and synovial procalcitonin in acute arthritis: a prospective study of 42 patients. *Clin Exp Rheumatol.* 2005;23:303-10.
- 58 Delevaux I, Andre M, Colombier M, Albuissou E, Meylheuc F, Begue RJ, et al. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? *Ann Rheum Dis.* 2003;62:337-40.
- 59 Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower respiratory tract infections in the community. *Lancet.* 1993;341:511-4.
- 60 Dixon RE. Economic costs of respiratory tract infections in the United States. *Am J Med.* 1985;78:45-51.
- 61 Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med.* 2001;163:1730-54.

- 62 Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Ortvist A, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J*. 2005;26:1138–80.
- 63 Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:2435.
- 64 Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, Saikku P. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax*. 2001;56:296–301.
- 65 Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–82.
- 66 Schuetz P, Koller M, Christ-Crain M, Steyerberg E, Stolz D, Muller C, et al. Predicting mortality with pneumonia severity scores: importance of model recalibration to local settings. *Epidemiol Infect*. 2008;1–10.
- 67 Marshall JC. Biomarkers of Sepsis. *Curr Infect Dis Rep*. 2006;8:351–7.
- 68 Brunkhorst FM, Al-Nawas B, Krummenauer F, Forycki ZF, Shah PM. Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. *Clin Microbiol Infect*. 2002;8:93–100.
- 69 Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. *Intensive Care Med*. 2006;32:469–72.
- 70 Kruger S, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J*. 2008;31:349–55.
- 71 Haeuptle J, Zaborsky R, Fiumefreddo R, Trampuz A, Steffen I, Frei R, et al. Prognostic value of procalcitonin in Legionella pneumonia. *Eur J Clin Microbiol Infect Dis*. 2008.
- 72 Becker KL, Nylen ES, White JC, Muller B, Snider RH Jr. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab*. 2004;89:1512–25.
- 73 Christ-Crain M, Morgenthaler NG, Stolz D, Muller C, Bingisser R, Harbarth S, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. *Crit Care*. 2006;10:R96–103.
- 74 Christ-Crain M, Morgenthaler NG, Struck J, Harbarth S, Bergmann A, Muller B. Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. *Crit Care*. 2005;9:R816–824.
- 75 Hinson JP, Kapas S, Smith DM. Adrenomedullin, a multifunctional regulatory peptide. *Endocr Rev*. 2000;21:138–67.
- 76 Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin N-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. *Peptides*. 2001;22:1693–711.
- 77 Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, Eto T. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *BiochemBiophysResCommun*. 1993;192:553–60.
- 78 Linscheid P, Seboek D, Zulewski H, Keller U, Muller B. Autocrine/paracrine role of inflammation-mediated calcitonin gene-related peptide and adrenomedullin expression in human adipose tissue. *Endocrinology*. 2005;146:2699–708.
- 79 Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an Adrenomedullin precursor fragment in plasma of sepsis patients. *Peptides*. 2004;25:1369–72.
- 80 Van den Berghe G. Endocrine changes in critically ill patients. *Growth Horm IGF Res*. 1999;9(Suppl A):77–81.
- 81 Van den Berghe G. The neuroendocrine response to stress is a dynamic process. *Best Pract Res Clin Endocrinol Metab*. 2001;15:405–19.
- 82 Vanhorebeek I, Van den Berghe G. The neuroendocrine response to critical illness is a dynamic process. *Crit Care Clin*. 2006;22:1–15, v.
- 83 Christ-Crain M, Stolz D, Jutla S, Couppis O, Muller C, Bingisser R, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med*. 2007;176:913–20.
- 84 Schuetz P, Mueller B, Nusbaumer C, Wieland M, Christ-Crain M. Circulating levels of growth hormone predict mortality and complement prognostic scores in critically ill medical patients. *Eur J Endocrinol*. 2008.
- 85 Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. *Peptides*. 2005.
- 86 Muller B, Morgenthaler N, Stolz D, Schuetz P, Muller C, Bingisser R, et al. Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. *Eur J Clin Invest*. 2007;37:145–52.
- 87 Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, et al. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. *Chest*. 2007;131:1058–67.
- 88 Papassotiriou J, Morgenthaler NG, Struck J, Alonso C, Bergmann A. Immunoluminometric assay for measurement of the C-terminal endothelin-1 precursor fragment in human plasma. *Clin Chem*. 2006;52:1144–51.
- 89 Hensen A, Modin A, Weitzberg E. Increased concentrations of endothelin-1 messenger RNA in tissues and endothelin-1 peptide in plasma in septic pigs: modulation by betamethasone. *Crit Care Med*. 1996;24:1530–6.
- 90 Brauner JS, Rohde LE, Clausell N. Circulating endothelin-1 and tumor necrosis factor-alpha: early predictors of mortality in patients with septic shock. *Intensive Care Med*. 2000;26:305–13.
- 91 Tschakowsky K, Sagner S, Lehnert N, Kaul M, Ritter J. Endothelin in septic patients: effects on cardiovascular and renal function and its relationship to proinflammatory cytokines. *Crit Care Med*. 2000;28:1854–60.
- 92 Wanecek M, Oldner A, Sundin P, Alving K, Weitzberg E, Rudehill A. Effects on haemodynamics by selective endothelin ET(B) receptor and combined endothelin ET(A)/ET(B) receptor antagonism during endotoxin shock. *Eur J Pharmacol*. 1999;386:235–45.
- 93 Krejci V, Hildebrand LB, Erni D, Sigurdsson GH. Endothelin receptor antagonist bosentan improves microcirculatory blood flow in splanchnic organs in septic shock. *Crit Care Med*. 2003;31:203–10.
- 94 Oldner A, Wanecek M, Gojny M, Weitzberg E, Rudehill A, Alving K, Sollevi A. The endothelin receptor antagonist bosentan restores gut oxygen delivery and reverses intestinal mucosal acidosis in porcine endotoxin shock. *Gut*. 1998;42:696–702.
- 95 Iskit AB, Senel I, Sokmensuer C, Guc MO. Endothelin receptor antagonist bosentan improves survival in a murine caecal ligation and puncture model of septic shock. *Eur J Pharmacol*. 2004;506:83–8.
- 96 Schuetz P, Stolz D, Mueller B, Morgenthaler N, Struck J, Mueller C, et al. Endothelin-1 precursor peptides correlate with severity of disease and outcome in patients with community acquired pneumonia. *BMC Infect Dis*. 2008;8:22.
- 97 Schuetz P, Christ-Crain M, Morgenthaler NG, Struck J, Bergmann A, Muller B. Circulating precursor levels of endothelin-1 and adrenomedullin, two endothelium-derived, counteracting substances, in sepsis. *Endothelium*. 2007;14:345–51.
- 98 Christ-Crain M, Breidhardt T, Stolz D, Zobrist K, Bingisser R, Miedinger D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med*. 2008.
- 99 Muller B, Suess E, Schuetz P, Muller C, Bingisser R, Bergmann A, et al. Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. *J Intern Med*. 2006;260:568–76.
- 100 Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Muller B. Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: an observational study. *Crit Care*. 2005;9:R37–45.
- 101 Luthold S, Berneis K, Bady P, Muller B. Effects of infectious disease on plasma lipids and their diagnostic significance in critical illness. *Eur J Clin Invest*. 2007;37:573–9.
- 102 Schuetz P, Christ-Crain M, Muller B. Biomarkers to improve diagnostic and prognostic accuracy in systemic infections. *Curr Opin Crit Care*. 2007;13:578–85.
- 103 Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341:515–8.
- 104 Moya F, Nieto A, Jil RC. Calcitonin biosynthesis: evidence for a precursor. *Eur J Biochem*. 1975;55:407–13.
- 105 Aouifi A, Piriou V, Bastien O, Blanc P, Bouvier H, Evans R, et al. Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients. *Crit Care Med*. 2000;28:3171–6.
- 106 Roos BA, Huber MB, Birnbaum RS, Aron DC, Lindall AW, Lips K, Baylin SB. Medullary thyroid carcinomas secrete a noncalcitonin peptide corresponding to the carboxyl-terminal region of preprocalcitonin. *J Clin Endocrinol Metab*. 1983;56:802–7.
- 107 Chesney RW, McCarron DM, Haddad JG, Hawker CD, DiBella FP, Chesney PJ, Davis JP. Pathogenic mechanisms of the hypocalcemia of the staphylococcal toxic-shock syndrome. *J Lab Clin Med*. 1983;101:576–85.
- 108 Hugle T, Schuetz P, Mueller B, Laifer G, Tyndall A, Regenass S, Daikeler T. Serum procalcitonin for discrimination between septic and non-septic arthritis. *Clin Exp Rheumatol*. 2008;26:453–6.
- 109 Gruber M, Christ-Crain M, Stolz D, Keller U, Müller C, et al. Prognostic impact of plasma lipids in patients with lower respiratory tract infections – an observational study. *Swiss Med Wkly*. 2009;139(11–12):166–72.