

REVIEW

Current status of procalcitonin in the ICU

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Keywords - Sepsis, severe sepsis, procalcitonin, pneumonia, bacterial infections, mycoses**Abstract**

This review outlines the main indications for the measurement of procalcitonin (PCT) on the intensive care unit (ICU): diagnosis or exclusion of sepsis (severe sepsis, septic shock) and assessment of severity and course of sepsis-related systemic inflammation, control of focus and response to antibiotic therapy. Follow up measurements of PCT are frequently done on the ICU and recommended to individualize decisions regarding the indication and duration of antibiotic therapy. Studies related to this topic and also the practical experience with the routine use of this marker as a guide to treatment are summarized in this review. Furthermore, conditions, which may increase PCT independently from sepsis, are prevalent in ICU patients and will also be discussed.

Use of PCT as a sepsis marker on the ICU

PCT has been recognized as a marker of sepsis since 1993.¹ Initially, PCT was mainly used for the diagnosis of (bacterial) sepsis and for the differential diagnosis of a bacterial versus non-bacterial aetiology of systemic inflammation. In the meantime, indications have been extended to a more dynamic use, e.g. to follow up and guide sepsis-related therapy, including antibiotic treatment and focus control – both in outpatients and ICU patients. The uniform induction during sepsis, the correlation of concentrations with severity of inflammation (high levels in patients with severe sepsis), the relative specificity for bacteria-induced systemic inflammation and a short half-life of induction and elimination fitting the needs of daily routine diagnostics support the clinical use of PCT as a biomarker on the ICU.

Biochemistry and induction

PCT is produced by the organism and therefore an indirect or host-response related biomarker of systemic inflammation, mainly induced by microbial infection (sepsis, severe sepsis, septic shock). The 114-116 amino acid protein and its shorter calcitonin-N-ProCT fragments are measured by the presently

available diagnostic tests. The protein is induced within several hours (3-6 hrs, peak 12-24 hours) after the respective stimulus (e.g. endotoxemia, sepsis, systemic inflammation and various proinflammatory mediators). Peak levels decline with a 50% plasma disappearance rate of roughly 1,5 days and somewhat more in patients with severe renal dysfunction. The normal range of PCT in healthy individuals is quite low (< 0.1 ng/ml), so that as the reference range for diagnosis of sepsis, concentrations above 0.25 - 0.5 ng/ml are usually used. When deciding on antibiotic therapy, the lower threshold with higher sensitivity is usually used. The protein has various biological functions, e.g. chemotactic effects on monocytic cells and modulation of expression of inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells. These functions are partially time-dependent and they are different in native and prestimulated cells. PCT neutralisation affects survival and organ dysfunction in animal septic shock models. PCT can be produced by adherent (not circulating) activated monocytes and tissue cells, where induction is augmented by a crosstalk of invading monocytic cells with adipocytes, as demonstrated by *ex vivo* experiments.² Also, the liver obviously plays a major role in PCT induction.^{3,4}

PCT can be induced by a variety of non-septic conditions as well, e.g., during cardiogenic shock, in patients with severe renal or hepatic dysfunction, after major surgery, in patients with severe systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), as well as in severe pancreatitis or during release of proinflammatory cytokines.⁴ However, as compared to severe sepsis, induction in these cases is often moderate (usually < 2 ng/ml) and – if related to a specific event – for a short period of time only (1-2 days). However, conditions inducing PCT without sepsis are more frequent in ICU patients and hence should be considered (*table 1*). In addition, in patients with local infection or those with a weak systemic inflammatory response, PCT levels may remain low. In patients with neutropenia or those under immunosuppression (e.g. corticosteroids) suppression of PCT is only moderate.

Table 1. Conditions, which may induce PCT other than bacterial infection

Condition	Expected Peak (approx.)	Estimated range	Reference
Postsurgical, posttraumatic Non-abdominal trauma or surgery: low or no PCT induction. Abdominal or retroperitoneal surgery/ trauma, thoracic surgery	Peak levels on day 1, rapidly declining If PCT is increased above the expected typical range, postoperative complications are more frequently observed	< 1 ng/ml for peripheral, non-abdominal trauma or minor abdominal surgery) < 2 ng/ml for abdominal surgery or trauma, cardiac surgery. 2 ng/ml is possible in patients with extended retroperitoneal or major abdominal surgery, liver transplantation	9, 78-82
Cardiogenic shock	Initially no increase. Increasing levels after 1-3 days, if high dose catecholamines are required	May be intermediate to high (e.g. > 0.5 ng/ml to > 10 ng/ml)	83-85
MODS, severe SIRS Pancreatitis, severe	Increasing slowly with severity Initially; normal PCT indicates mild or oedematous pancreatitis. Increasing levels related with severity, organ dysfunction and necrosis	> 0.5 ng/ml - > 10 ng/ml < 0.2 ng/ml: mild or oedematous pancreatitis. In patients with severe pancreatitis: 0.5 ng/ml - > 10 ng/ml	17, 86, 87 53, 54, 58, 59
Autoimmune disorders	Usually not elevated in: Rheumatoid arthritis, chronic arthritis, systemic sclerodermia, amyloidosis, thyreoiditis, psoriasis, inflammatory bowel disease, systemic lupus erythematosus. Can be elevated in Kawasaki Syndrome, Goodpasture's Syndrome, Anti-neutrophil antibody-positive vasculitis, autoimmune hepatitis or primary sclerosing cholangitis, M. Still	In most autoimmune disorders no or minor induction of PCT only (0.1-1 ng/ml). Some induce significant PCT levels of > 1 ng/ml -10 ng/ml (see left column)	88-94
Severe renal dysfunction	If decompensated or end stage disease only, or haemodialysis.	In the lower range, 0.1-2 ng/ml, constant elevation	27, 95-98
Severe liver dysfunction	Chronic, Child C only In some cases increased level in patients with acute liver failure	In chronic disease in the lower range, 0.1-2 ng/ml, constant. In acute cases higher levels reported	99
After prolonged resuscitation	Peak day 1	In case of prolonged CPR, levels are related with prognosis	100, 101
Heat Shock	Acute	High concentrations reported	102, 103
New-born first days of life	Peak day 1-2	Use adapted reference range	104-106
Paraneoplastic		Very rare, except MCT	107
OKT-3, Anti Lymphocyte Antigens	Acute	Medium range, low if pre-treatment with corticosteroids	108-110
End stage of tumour disease	Chronic	Low (0.5-2 ng/ml)	42
Rhabdomyolysis	Acute	May be very high	Individual reports
Severe burns, inhalation trauma, aspiration.	First days and during severe SIRS or infection	Follow up recommended	111-114

PCT and other presently used markers of sepsis

The diagnosis of sepsis and monitoring of therapy could be improved if PCT measurements were added to the clinical and conventional signs of sepsis.⁵ PCT has different properties when compared with CRP or lactate – markers which are often recommended for diagnosing sepsis. CRP, for example, has a low specificity for sepsis and concentrations do not indicate the risk and severity of sepsis well.⁶⁻⁸ It responds late and plasma levels may be affected by immunosuppression. A decline of CRP towards the normal range may take from several days up to one week. At the acute onset of sepsis or severe sepsis, some patients may present with a moderate increase of CRP only (e.g. 50-100 mg/l) which may not reflect the progression or severity of the disease. Such levels can also be observed in various other ICU patients, e.g. post-surgical. In contrast, high CRP levels (e.g. > 300 mg/l) are also induced after major surgery, especially major abdominal or retroperitoneal surgery in patients without sepsis.⁹ Thus, it is difficult to draw therapeutic conclusions from

CRP levels on the ICU. This may lead to under recognition of sepsis by CRP in an acute situation.

Lactate is primarily a marker of cellular and oxidative metabolism and perfusion and hence an epiphenomenon of sepsis only. Significantly increased or high levels of lactate mainly occur in patients with severe or progressive stages of sepsis, e.g. if severe organ dysfunction or septic shock are already present. To significantly affect the outcome, sepsis must be recognized and treated early – at best prior to the onset of shock or organ dysfunction. Furthermore, lactate does not differentiate septic from nonseptic shock.¹⁰

Other markers like fever, leukocytes, blood sedimentation rate, coagulation parameters, thrombocytes, acute phase proteins and pathogen-associated molecules like endotoxin and PCR based methods may be useful for the diagnosis of sepsis as well. First, as an early sign of sepsis suspected by routine diagnostics measured for other indications (like thrombocytes and coagulation parameters) or as a supplemental marker, but

most of these markers lack specificity and their ability to assess the risk, severity and course of the disease is often poor.

Due to the distinct profile of PCT as compared to these markers, PCT is used in a number of ICUs as a biomarker of sepsis – along with a variety of other signs of sepsis e.g. those from routine measurements – and is often included in the daily routine and clinical rounds, since diagnostic and therapeutic decisions are influenced by this marker, e.g. the assessment of efficacy of therapeutic measures.

Indications and measurement of PCT on the ICU

Indications for PCT measurement on the ICU basically do not differ from indications in other patients. However, different from the emergency department, consecutive measurements are most frequent on the ICU. This means that patients can be monitored and any unnecessary antibiotic use can be limited. Single or semi-quantitative measurements for differential diagnosis are far less useful on the ICU. Indications are summarized in *table 2*.

Confirmation or exclusion of the diagnosis of sepsis, severe sepsis, septic shock

The major strength of PCT is its high positive predictive value to rule in the diagnosis of sepsis, severe sepsis or septic shock and its high negative predictive value (in case of normal or low PCT plasma concentrations) to exclude a severe SIRS, mainly due to bacterial infection (*table 3*). Also, the probability for bacteraemia is significantly increased in patients with higher PCT levels or reduced in case of normal PCT.¹¹⁻¹³ This finding has been confirmed by various publications and it has been

Table 2. Indications for PCT-guided monitoring of treatment on the ICU

<ul style="list-style-type: none"> • To confirm or exclude diagnosis of sepsis, severe sepsis, septic shock (including differential diagnosis) • Assessment of severity of systemic inflammation, caused by sepsis (severe sepsis/septic shock), reflecting the risk of organ dysfunction and mortality. The need of urgent interventions thus can be better estimated • Follow up of systemic inflammation after focus removal or focus therapy, to assess efficacy of treatment • In patients with antibiotic treatment in order to better estimate the duration of therapy or to withhold or stop therapy, e.g. if there is no sepsis, if the focus has been cured. For related algorithm see below. Exclusion criteria should be obeyed. • To determine and monitor patients, who do not need antibiotics on the ICU, to exclude the risk of sepsis and life-threatening systemic infection and bacterial infection. In case of persistent elevated PCT: diagnosis and therapy should be re-evaluated.
<p>For specific indications:</p> <ul style="list-style-type: none"> • In patient with pancreatitis: to early asses severity and infection • To support or exclude diagnosis of bacterial infection with high or low probability, e.g. bacterial meningitis, bacteraemia, peritonitis, sepsis from urinary tract infection. • If there is no response of PCT levels to antibiotic therapy: fungal infection or other diagnosis may be present (PCT often 1-5 ng/ml) • PCT can also be used in out-patients for indication and monitoring of antibiotic therapy, mainly in patients with respiratory tract infections.

Table 3. PCT levels in patients with bacterial infection and various severity of systemic involvement

SIRS Median (*), range Mean (+), SD	Sepsis	Severe sepsis	Septic shock	Reference, number of observations
--	2.4 ± 0.5 (+)	37 ± 16	45 ± 22	(69) n = 145
0.6 ± 2.2 (+)	6.6 ± 22.5	--	35 ± 68	(70) n = 337
1.3 ± 0.2 (+)	2.0 ± 0	8.7 ± 2.5	39 ± 5.9	(71) n = 100
< 0.5 ng/ml (*)	0.8 ng/ml	--	4.3 ng/ml	(7) n = 190
3.8 ± 6.9 (+)	1.3 ± 2.7	9.1 ± 18.2	38 ± 59	(72) n = 101
3.0 (0.7-29.5) (*)	--	19.1 (2.8-351)	16.8 (0.9-351) „all septic patients“	(73) n = 33
0.5 ± 0.2 (+) (approx.)	2 ± 2 (approx.)	18 ± 10 (approx.)	20 ± 10 (approx.)	(74) n = 101
0.38 (*) (0.16-0.93 quartiles)	3.0 (1.48-15)	5.58 (1.84-33)	13.1 (6.1-42)	(6) n = 101
0.6 (0-5.3) (*)	3.5 (0.4-6.7)	6.2 (2.2-85)	21.3 (1.2-654)	(5) n = 78

implemented in guidelines and the FDA-approval in the USA.¹⁴⁻¹⁶ High PCT levels are also related to a high risk of organ dysfunction and mortality due to sepsis.¹⁷⁻²¹ However, local bacterial infection or bacterial colonisation cannot be excluded by PCT. Fungal infection, when complicated by systemic inflammation, may also induce PCT. These patients frequently have PCT levels in a medium elevated range only (1-5 ng/ml) or they do not respond to antibiotic therapy.²² Typically these patients have a high risk profile. Therapy should be started early if there is suspicion. A rapid decline after antifungal therapy has been reported.²²⁻²⁴

Local infection

Local bacterial infection or bacterial colonisation usually do not induce PCT. Even in patients with acute appendicitis, acute cholecystitis even with local peritonitis the PCT response may be weak. This should be known and hence diagnosis or therapy should not be excluded by a low PCT. Interestingly, a conservative treatment of less severe appendicitis has recently been discussed as well.^{25,26} On the contrary, high PCT levels in a patient with appendicitis or local peritonitis is undoubtedly a sign for urgent intervention.

The information of normal PCT levels on the ICU has various consequences: for example, microbial findings may be interpreted as local infection or bacterial colonisation only and antibiotic treatment may not be necessary. Further, invasive or non-invasive diagnostic or therapeutic interventions may not be urgently needed, since the diagnosis of sepsis is unlikely and the sepsis-related risk of organ dysfunction and mortality are low.

PCT elevation in patients without sepsis

Moderately increased PCT levels in patients without sepsis have been observed at various conditions. Usually, PCT levels in these cases are not very high (< 2 ng/ml) and induction

is short (1-2 days) and often related to a specific event. Such conditions are more frequently seen on the ICU than in the average population. The ICU physician should know this and interpret PCT values accordingly (*table 1*). However, decisions made on an increase of PCT that are not related to sepsis should be done by exclusion. Primarily, every increase should be interpreted first as a possible sign of sepsis, until a follow up and further clinical examination have excluded this diagnosis and levels can be explained otherwise. Undoubtedly, this is a grey area, since at the acute onset of sepsis, in patients without organ dysfunction and during early stages of sepsis or in patients with respiratory tract infections or pneumonia even a small increase of PCT is important for the diagnosis of sepsis (e.g. PCT > 0.25 ng/ml).

Depending on the type of ICU, postsurgical and posttraumatic induction of PCT can frequently be observed, mainly following abdominal surgery or abdominal trauma. Induction may also relate to severe SIRS and MODS, e.g., in patients with prolonged cardiogenic shock requiring catecholamines. Then, the initial concentration may be low, but it may increase during the following days sometimes even to high levels (>10 ng/ml). In patients with severe renal or liver dysfunction, a moderate, but constantly elevated basal level can be seen and, usually, concentrations do not exceed 1-2 ng/ml. PCT induced by heat shock, rhabdomyolysis and some specific types of autoimmune disorders as well (especially those where monocytic cells are involved) and concentrations can be quite high. Endotoxemia or bacterial translocation may explain induction in some patients with prolonged cardiogenic shock, abdominal trauma or surgery, severe acute liver dysfunction or severe MODS. In other patients, severe tissue trauma and invasion of monocytic cells or exposure to proinflammatory cytokines may explain induction of PCT.

Usually, follow up of measurements in relation to a specific event (e.g. surgery, trauma), or non-responsiveness to therapeutic interventions (e.g. in cases of severe chronic renal or liver dysfunction) point to induction of PCT independently of sepsis.

Severity and course assessment: inflammation monitoring

Assessment and monitoring of the course and severity of the SIRS is a major indication for the measurement of PCT on the ICU. PCT levels are a mirror of the activity of SIRS in patients with sepsis (*table 2*). The 50% plasma disappearance rate of about 1,5 days for PCT as previously mentioned allows a daily follow up for monitoring of the patient.²⁷ Even if the correlation with disease severity is rather a qualitative than a quantitative one and a gold standard is missing, high PCT levels (e.g. concentrations from 2-10 ng/ml) usually indicate severe systemic inflammation with high probability of organ dysfunction.

Very high peak levels (> 100 ng and even more than 1000 ng/ml) are mostly transient and last for only 1-2 days; they are usually seen at the acute onset of inflammation only. If immediate therapy is effective, such high concentrations may not necessarily indicate a fatal prognosis. For example, in patients with pyelonephritis and urosepsis, high concentrations have often been observed, but patients most frequently have a good prognosis, if therapy starts immediately.²⁸ Similarly, a significant decline most often indicates resolution of the disease.^{29,30} But on the contrary, if treatment is not effective and PCT levels remain elevated, then the mortality rate is increased.^{5,17,29,31,32}

If the infection focus has been cured and the sepsis disappeared (as confirmed by low PCT), antibiotics can often be stopped earlier than recommended by general guidelines, which do not consider individual responses.^{33,34} If there is no decline of the systemic inflammatory response, then re-evaluation of the working hypothesis or therapy is recommended.

Antibiotic stewardship: PCT-guided antibiotic therapy

Increasing evidence has been compiled that PCT can be used to guide antibiotic therapy, leading to individualized or shorter antibiotic treatment courses as compared to a fixed standard regimen, also in patients on the ICU. On average, a 2-3 day reduction of antibiotic therapy has been reported (*table 4*). Most of the patients in these studies had acute respiratory tract infections, although this approach has been used for other infections and patients with sepsis and severe sepsis as well. Various, albeit basically similar, algorithms have been used. Some include both a fixed cut-off value and evaluation of the kinetics. No negative side effects have been reported so far, but there is on-going criticism that the statistical power to rule out significant effects on mortality is low and that mainly patients with lower respiratory tract infections have been investigated.³⁵ So far, 3691 patients have been investigated in randomized clinical trials, of whom 166 died in control groups and 159 in PCT-guided groups, confirming non-inferiority of the latter strategy by excluding an effect on mortality below 8-10%.³⁵ With a computer based model and analysis of retrospective ICU data from 1312 patients, a virtual use of the PCT-guided algorithm resulted in substantial reduction of treatment costs, based on the German diagnosis-related groups calculation.³⁶ In the Netherlands, a prospective study using a PCT-guided algorithm for the management of antibiotic therapy is underway.³⁷

Effects on microbial resistance rate have also been postulated, but this has not been confirmed yet. Usually, less antibiotic treatment is related with less microbial resistance and less antibiotic-related side effects. Thus, the beneficial effect of this approach may surpass the reduction of antibiotic consumption. All patients receiving antibiotics on the ICU should be evaluated daily by PCT. We nevertheless recommend that

Table 4. Randomized controlled trials using PCT-guided algorithms to guide antibiotic therapy report a shorter and patient-adapted, individualized antibiotic treatment

Patients included	PCT Algorithm	Result	Reference
Community acquired pneumonia (CAP)	PCT <0.1 ng/ml: Severe bacterial infection unlikely, prescription of antibiotics not recommended (strong recommendation) PCT 0.1-0.25 ng/ml: Bacterial infection requiring therapy is not likely: antibiotic therapy is not recommended PCT 0.25-0.5 ng/ml: Bacterial infection requiring therapy may be present: antibiotic therapy recommended PCT >0.5 ng/ml: Bacterial infection requiring therapy is likely: antibiotic therapy is recommended (strong recommendation) For patients already taking antibiotics upon admission: if PCT <0.25 ng/ml: discontinuation of antibiotics recommended.	Shorter duration of treatment in the PCT group: 5 days vs. 12 days (median of study/control group)	(33) n = 302
Severe sepsis, septic shock	For an initial or „peak“ value of ≥ 1 ng/ml: Follow up on day 5. End of antibiotic treatment if PCT < 10% of the initial value or absolute value < 0.25 ng/ml For an initial/peak value <1 ng/ml: check on day 3: End of antibiotic treatment if PCT < 0.1 ng/ml. If blood culture Positive: Treatment at least 5 days.	Shorter duration of Antibiotic treatment: 6 days vs. 9.5 days (median of study/control group)	(75) n = 79
Patients in operative Intensive care with sepsis (at least 2 SIRS criteria = Severe sepsis, septic shock)	Discontinuation of antibiotic therapy after Reduction in clinical signs of infection and PCT ≤ 1 ng/ml or – if initial value >1 ng/ml – if reduction after 3 days to 25-35% of the starting level (equivalent to an decrease of more than 65-75% in 3 days)	Shorter duration of antibiotic Treatment in the PCT group (5.9 ± 1.7 vs. 7.9 ± 0.5 days) Shorter duration of intensive care Treatment in the PCT Group	(76) n = 110
Patients with severe sepsis	Discontinuation of antibiotic therapy if regression of clinical signs of infection and PCT ≤ 1 ng/ml or (if PCT >1 ng/ml) if decrease after 3 days to 25-35% of the baseline value.	Reduction of treatment 1.7 days in the PCT group (6.6 ± 1.1 vs. 8.3 ± 0.7 days)	(77) n = 27
Patients in intensive care with suspected infections, multicentre study	For algorithm, see <i>figure 1</i> .	Antibiotic-free days: PCT: 14.3 ± 9.0 days, control: 11.6 ± 8.2 days (23% relative reduction in antibiotic exposure), no difference In mortality (28 days)	(34) n = 621
Ventilator-associated Pneumonia (VAP), 5 centres	PCT after 72 hours: < 0.25 ng/ml or PCT >0.25 ng/ml to <0.5 ng/ml or more than 80% decrease compared with day 0: discontinuation of antibiotic therapy is recommended (strong or less strong recommendation, respectively). PCT 0.5 ng/ml or less than 80% decrease or PCT >1 ng/ml: discontinuation of antibiotic therapy is not recommended (level of recommendation, less strong or strong, respectively). Daily re-evaluation after 72 hours.	Antibiotic-free days: 13 days (PCT) vs. 9.5 days (control group), 27% relative reduction in antibiotic treatment (study primary end point). Secondary end points (risk assessment): no differences between the groups (mortality, treatment days with ventilation or in intensive care)	(65) n = 101

further information is documented and included into decision making on treatment. This includes clinical data regarding the success of treatment of the infection focus and related data (physical, biochemical and clinical signs and symptoms). Also, the general situation of the patient should be taken into account, as for example the presence or absence of organ dysfunction and sepsis. The expertise of the treating subspecialty (e.g. abdominal surgery) should also be taken into account. The decision to stop, change or continue antibiotics should thus be done by the medical team in a consensus decision.

In our ICU we use a checklist with documentation of both PCT, microbiological data and a selection of further focus-related and clinical data to increase patient safety. All decisions are discussed with the medical team and the decision is documented. PCT-guided recommendations are based on the algorithm of Bouadma (*figure 1*).³⁴ In the checklist,

source, signs and symptoms of infection and successful or unsuccessful treatment of the focus, the presence or absence of sepsis and organ dysfunction, PCT values and the algorithm based recommendation and possible exclusion criteria are documented. All criteria are re-evaluated daily with regard to three main issues. (i) Efficacy at the onset of therapy (on day 1-3 of antibiotic treatment). If there is a response to therapy, antibiotics are continued. (ii) After day 3, latest on day 7: the recommendation to stop therapy (if there is no sepsis and no acute organ dysfunction anymore and the focus has been eliminated and PCT is low according to the algorithm). Most frequently this is possible between days 3-6 after onset of therapy. (iii) Re-evaluation of therapy, if treatment has not been effective according to these criteria. Lastly, on day 7 we suggest a final stop and basic reevaluation of antibiotic therapy. If antibiotics are continued then the reasons must be discussed

Figure 1. Example of an algorithm for an individual guide for antibiotic therapy according to ref. 34

Guidelines for initiating antibiotics according to PCT value. Except any situation requiring immediate therapy ...			
PCT...			
< 0.25 ng/ml	0.25 - 0.5 ng/ml	0.5 - < 1.0 ng/ml	≥ 1.0 ng/ml
Antibiotics strongly discouraged	Antibiotics discouraged	Antibiotics encouraged	Antibiotics strongly encouraged
Guidelines for stopping, continuing or changing antibiotics according to daily measured PCT value.			
PCT ...			
< 0.25 ng/ml	Decline more than 80% or 80% of peak (maximum) value or ≥ 0.25 to < 0.5 ng/ml	Decline of PCT less than 80% of peak value and PCT ≥ 0.5 ng/ml	Increase of PCT above previous and PCT ≥ 0.5 ng/ml
Stopping antibiotics strongly discouraged	Stopping antibiotics encouraged	Continuing antibiotics encouraged	Changing antibiotics strongly encouraged

and documented. Exclusion criteria for this approach must be known (e.g. therapy for local infection, when necessary, e.g. in case of local destructive infection like endocarditis, infection of cerebral drainage, bone or cartilage, impaired immunologic function e.g. in patients with severe SIRS or MODS or infection with specific and aggressive pathogens like tuberculosis and other potentially harmful microbial species). Using team-based decisions combined with clinical evaluation of the patient rather than the PCT-based algorithm alone, we did not observe significantly negative side effects in individual patients despite a significant number of patients not treated by antibiotics in our ICU.

Specific indications

Bacteraemia

On average, in patients with bacteraemia, often higher PCT levels have been reported as compared to patients with negative blood cultures. Also the negative predictive value of low PCT levels to exclude bacteraemia is high.^{11,12,38-42} If PCT had been used as a single decision tool, as reported in a group of patients with urosepsis, for example, 40% fewer blood cultures would have been taken, whereas 94-99% of patients with bacteraemia would still be correctly diagnosed (with PCT >0.25 ng/ml).¹³ However, some patients with positive blood cultures may have low or normal PCT values as well, since PCT is a marker of the individual immune response to infection which may be weak even during bacteraemia.

Meningitis

In patients with acute bacterial meningitis, various studies have reported high PCT levels, most often higher than 0.5 ng/ml. In patients with viral meningitis, PCT levels were found to be barely elevated.⁴³⁻⁴⁶ This information was used to reduce antibiotic treatment during epidemic outbreaks.⁴⁷⁻⁴⁸ Although the initial antibiotic therapy was given to all patients (since there may be false negative results), duration of therapy could be significantly reduced using serial measurements of PCT. In patients with sub acute or local infection, e.g. infection of an

internal or external ventricular drainage, PCT levels do not respond sufficiently.⁴⁹ Infection monitoring of patients with ventricular drainage by PCT is thus not recommended. Also, measurement of PCT in the cerebral fluid is not indicative.

Endocarditis

In patients with bacterial endocarditis, PCT levels are usually elevated. Median values on admission were 3.5 ng/ml in a study from Kocazeybek et al. (50 patients)⁵⁰ and 6.5 ng/ml in another study by Mueller et al.⁵¹ However, similarly as in patients with bacteraemia, PCT may be low in patients with bacterial endocarditis, e.g. if the systemic inflammatory response is not activated.⁵² Hence, echocardiography is still the gold standard. However, also on the ICU, patients with elevated PCT levels may have endocarditis and this focus should also be excluded in cases of increased PCT. In our ICU, we have several case reports of patients, primarily presenting with unspecific symptoms, cardiogenic shock or fever but with increased PCT, where endocarditis was diagnosed early following an elevated PCT.

Pancreatitis

PCT may indicate severity of acute pancreatitis: if initial PCT levels are low (< 0.2 ng/ml) this is more frequently due to oedematous or mild pancreatitis only.⁵³⁻⁵⁶ Whether antibiotic therapy is required in these patients has not yet finally been decided upon, but it may not be necessary if there is no sepsis and PCT is low. During the course of the disease, high PCT levels are more frequently seen in patients with severe pancreatitis and infected necrosis.⁵⁷⁻⁵⁹ To assess severity, PCT seems to be equivalent to various scoring systems.⁶⁰ Discriminating infected versus non-infected necrosis, however, is not possible by PCT levels, since severe pancreatitis also induces PCT.^{61,62}

Pneumonia

In patients with pneumonia, increased PCT levels may be expected as well, but plasma levels may not be very high in all

patients. Even in patients with bacterial pneumonia, depending on the patients analysed, in up to one third of patients with bacterial pneumonia, PCT in the lower range has been reported, whereas in approximately another third PCT was high. Normal or low PCT values were also reported in patients with viral or atypical pneumonia. Nevertheless, measurement of PCT in patients with pneumonia is recommended – not as a primary diagnostic tool, but to follow up and assess efficacy of treatment, both in patients with community-acquired (CAP) and ventilator-associated pneumonia (VAP). Various studies indicate that declining PCT levels in patients with pneumonia indicate a favourable prognosis, whereas persistently elevated PCT levels were more frequently observed in patients with a fatal course.^{29,63} In other studies, the duration of antibiotic treatment in patients with CAP and VAP was shorter when PCT-guided-algorithms were used instead of fixed treatment courses.^{33,34,64,65} An individual approach to therapy in patients with pneumonia is recommended, since pneumonia is a very heterogeneous disease, with various aetiology, associated pathogens, severity and patients' risk profile. This recommendation to use a PCT-guided approach is part of the German guideline for the treatment of lower respiratory tract infection and CAP.⁶⁶ In various constellations, short treatment courses with antibiotics are sufficient in some patients without major risk factors and less severe disease.^{67,68} PCT measurement supported these individual decisions, if specific PCT-dependent algorithms were included in the therapeutic approach in patients with CAP and lower respiratory tract infections.^{33,34,64}

In conclusion

Daily quantitative measurement of PCT is recommended on the ICU in all critically ill patients with a suspected diagnosis of systemic inflammation, after focus removal and during antibiotic therapy to monitor systemic inflammation and success of therapy. This approach affects therapeutic and diagnostic decisions, if plasma levels are interpreted together with other clinical data. Further indications for measurement of PCT in the ICU are related to specific questions, e.g., the diagnosis of bacterial sepsis, meningitis, diagnosis of a possible focus of infection e.g. endocarditis, assessment of the presence and severity of systemic inflammation e.g. in patients with pancreatitis or as an additional tool to exclude severe systemic inflammation in patients with primary local infection or bacterial colonisation. To guide antibiotic therapy, PCT can be used not only in patients with lower respiratory tract infections and CAP but also in sepsis and severe sepsis of different aetiology on the ICU, resulting in shorter treatment courses without harming the patient, this in accordance with currently available evidence.

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