Update on Procalcitonin Measurements

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Procalcitonin (PCT) is used as a biomarker for the diagnosis of sepsis, severe sepsis and septic shock. At the same time, PCT has also been used to guide antibiotic therapy. This review outlines the main indications for PCT measurement and points out possible pitfalls.

The classic indications for PCT measurement are: (i) confirmation or exclusion of diagnosis of sepsis, severe sepsis, or septic shock, (ii) severity assessment and follow up of systemic inflammation mainly induced by microbial infection, and (iii) individual, patient adapted guide of antibiotic therapy and focus treatment.

Using serially monitored PCT levels, the duration and need of antibiotic therapy can be better adapted to the individual requirements of the patient. This individualized approach has been evaluated in various studies, and it is recommended to be a part of an antibiotic stewardship program.

Procalcitonin (PCT) as a marker for the diagnosis of sepsis and to guide antibiotic therapy

PCT has the highest accuracy for the diagnosis of sepsis in various settings. The lag time for PCT induction is approximately 2 to 4 hr after the onset of sepsis, a time period that has usually passed if patients are presented at the emergency department (ED).

Peak levels of PCT occur at 24 to 48 hr after sepsis. Early treatment of sepsis is most effective ("the golden hours of treatment"), and complications like organ dysfunction indicate an already progressed state of the disease.

Therefore, early confirmation of systemic inflammation and sepsis, as done by PCT measurement, is most important. Various studies have confirmed that survival rate of patients with sepsis can be significantly improved if antibiotic therapy is initiated immediately using the right antibiotics [1].

Point-of-care (POC) tests, despite being semi-quantitative, are helpful in situations when quantitative measurements are not going to be available within reasonable time (1-3 hr).

However, a semi-quantitative POC test should be sensitive enough to indicate or exclude systemic inflammation. This usually requires a lower assay sensitivity of 0.2-0.3 ng/mL. If the clinical impression indicates a possible diagnosis of sepsis, but PCT levels are not elevated, patients should still be treated for sepsis initially, regardless of the high negative predictive value of normal PCT.

Monitoring patients during the next one to two days will indicate whether the initial diagnosis is correct and antibiotics can be discontinued early if sepsis is excluded and PCT remains low. This approach is also supported by the society of critical care medicine (SCCM) sepsis guidelines [2]. PCT is also a food and drug administration (FDA)-approved diagnostic marker.

PCT has also proved to be useful in guiding antibiotic therapy. This approach was mainly evaluated in patients with respiratory tract infections; however, it can also be used in critically ill patients with sepsis or severe sepsis of various origins [3-7].

In addition, in outpatients with respiratory tract infection and exacerbation of chronic obstructive pulmonary disease (COPD), antibiotic prescription rates were significantly reduced by the use of PCT [8, 9]. This diagnostic approach is also recommended in various guidelines [10, 11].

Induction and biochemical properties

PCT was described as a marker of sepsis in 1993 [12]. It is a soluble protein liberated into the circulation of patients in response to severe systemic inflammation, in particular by bacterial infection.

Biochemically, it is the prohormone of the hormone calcitonin, but the biological function and induction are different from that of calcitonin. The induction of PCT is more strictly regulated as compared to cytokines: there is no significant PCT production in stimulated whole blood, but PCT production has been observed in various tissues during sepsis.

The induction of circulating PCT is related to the activation and adherence of monocytic cells, which occurs during sepsis as well as in other conditions such as after tissue trauma. Adherent monocytes and adipocytes, when in contact with activated monocytes, have been shown to produce PCT *ex vivo* [13].

The role of liver during PCT induction has been demonstrated in a baboon endotoxin shock model, in which the PCT response was significantly attenuated after liver explantation [14]. This difference in regulation of induction may be one reason why PCT has a different profile than other markers of sepsis.

Diagnostic tests measure the calcitonin/N-ProCT part of the protein and hence only a fragment of the 114-116 amino acid chain of the prohormone. Plasma levels of PCT in healthy individuals are quite low (<0.1 ng/mL) [15].

To exclude sepsis and systemic inflammation, a concentration of ≤0.2 ng/mL is a useful reference range. As a cut-off for the diagnosis of sepsis, plasma levels of ≥0.5 ng/mL are interpreted as abnormal and suggest sepsis.

After reaching peak levels, the circulating PCT concentration declines with a 50% plasma-disappearance rate of roughly 1-1½ days. In patients with severe renal dysfunction, elimination rates may be prolonged (one third to one half), but accumulation of PCT does not occur.

Various biological functions of PCT have been described. These include modulation of immunologic functions and vasomotility. Some effects are time-dependent and different in normal and prestimulated cells.

For example, the migratory response of monocytic cells is augmented by PCT, but it gets inhibited after some hours of incubation with PCT [15]. Similarly,

expression of inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells is inhibited by PCT in native cells, but it is augmented in prestimulated cells [16, 17]. In addition, PCT has been shown to influence the expression of cytokines.

In experimental shock models, neutralization or injection of PCT had an impact on the survival and organ dysfunction in the hamster and porcine animals, but injection of PCT into sham animals was found to have no effect. Hypothetically, these effects of PCT may contribute to the different local and systemic response of perfusion and inflammation of tissue observed in patients with sepsis.

Comparison with other markers of sepsis

PCT has a different profile than other presently used markers of sepsis, such as C-reactive protein (CRP), lactate, or various proinflammatory cytokines (interleukin (IL)-6, IL-8).

It also belongs to a different class of molecules, which may be called "hormokines," as suggested by Mueller *et al.* [18], which indicates the cytokine-like behavior of PCT during inflammation and infection. It is also a natural substrate for dipeptidyl-peptidase IV, which inactivates various cytokines [19].

The specificity of CRP for the diagnosis of sepsis is rather low and its peak plasma levels do not indicate the severity of systemic inflammation adequately. Hence, CRP concentrations can be misleading and may fail to diagnose severe sepsis [20-22].

CRP levels may also be significantly elevated in response to various types of stimuli, such as different types of trauma and inflammation, which may not necessarily be a case of severe infection or sepsis. For example, after both minor and major surgery, CRP levels may be elevated to >50 mg/mL [23].

However, there may be only a moderate increase of CRP level (50-100 mg/L or less) in patients with an acute onset of sepsis or even severe sepsis. This may lead to inappropriate treatment due to which fatal consequences have been reported.

Finally, not only does the increase to peak levels of CRP may take several days, the decline of its increased plasma levels may also take up to one or two weeks. As a result, CRP is not considered to be a useful marker in the intensive care unit (ICU) and in critically ill patients.

Lactate is also frequently used as a biomarker for sepsis, severe sepsis, and septic shock. However, lactate is not an early indicator of sepsis and lacks specificity. It is primarily a marker of impaired oxidative metabolism or perfusion abnormalities, which may be an epiphenomenon of sepsis and organ dysfunction.

Several other conditions may also cause an increased lactate production or a decreased lactate clearance. Since perfusion abnormalities and impairment of oxidative metabolism are closely related to organ dysfunction, success of therapeutic interventions may already be limited, if lactate level has increased significantly (>4 mmol/L).

Lower levels of lactate (<2 mmol/L) are less specific and are more frequently seen in critically ill patients. In addition, lactate levels do not clearly differentiate a septic from a nonseptic shock [24].

Cytokines and various other novel and recently published markers of sepsis generally do not exhibit significant advantage over PCT measurement except for some specific features. They either do not indicate severity of systemic inflammation (e.g. the endotoxin activity assay, soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), and various acute phase proteins) or the relative specificity for bacterial induced sepsis is low (e.g. cytokines).

However, cytokines react immediately to severe systemic inflammation and hence do not have the disadvantages of CRP or lactate measurements. Cytokine levels are also increased in local effusions, which is usually not seen in case of PCT. High levels are correlated with the severity of systemic inflammation

and an impaired outcome (e.g. IL-6 levels >1,000 pg/mL and higher) [25, 26], but they lack specificity and peak levels may change rapidly without clinical correlation. Despite of this, in some patients, the quick response of IL-6, in terms of both increase and decrease, may provide additional information. In addition, these biomarkers have not been consistently investigated for their role as a guide to antibiotic therapy. Only some studies investigated this topic, and this is not evidence enough for a clinical routine use [27].

During routine clinical investigations, various other laboratory markers should be observed for an unexpected diagnosis of sepsis. For example, various coagulation parameters, D-dimers, thrombocyte and leukocyte counts, and temperature may indicate an unexpected onset of sepsis. A specific diagnosis can then be confirmed using more specific markers like PCT.

Diagnosis of sepsis, severe sepsis, and septic shock

High PCT levels have a high positive predictive value to rule in the diagnosis of sepsis, severe sepsis, or septic shock (PCT >0.5 to >2 ng/mL). On the contrary, normal or very low PCT plasma concentrations have a high negative predictive value to rule out severe systemic inflammation or sepsis (PCT <0.25 to <0.5 ng/mL).

These are the hallmarks of PCT diagnostics. The common link between PCT elevation and bacterial infection is the severity of systemic inflammatory response. Bacterial infection is a strong stimulus for PCT production whereas if the systemic inflammation is due to viral infection, the PCT induction is low [28-31]. Also in patients with SIRS, there may be PCT induction, but this is usually not as high as in severe sepsis.

In situations such as in patients with aneurysmal subarachnoid hemorrhage, the high negative predictive values of low PCT (<0.2 ng/mL) can be used to exclude an infection [32]. It is also important to note that various conditions other than bacterial infection may induce PCT elevation, for example, severe trauma, some autoimmune disorders, or prolonged cardiogenic shock.

On the other hand, a local bacterial infection does not induce significant amounts of PCT. In case of endocarditis, for example, PCT can be normal or elevated, depending on the systemic inflammatory response.

Similarly, PCT levels may be low, if there is no systemic inflammatory response in patients with bacteremia. However, patients with bacteremia usually have significantly high PCT levels and therefore, bacteremia is not very likely if PCT levels are found to be normal [33-35].

Severity of inflammation and follow-up of treatment

The severity of the systemic inflammatory response is roughly correlated with the severity of systemic inflammation, although a gold standard is missing. Usually, high PCT levels are found in patients with severe sepsis and septic shock.

The elevated as well as highly elevated level of PCT (>2 ng/mL or >10 ng/mL, respectively) is a sign of alarm indicating a high risk of organ dysfunction due to systemic inflammation and calls for immediate treatment of the patient.

Depending on the success of therapy, high PCT levels are more frequently related to an increased mortality risk. Indeed, low PCT levels were related to a better outcome in patients with sepsis and infection as well as acute pancreatitis [36-39]. Importantly, the course of PCT levels over time, rather than absolute PCT values, affect the prognosis of systemic inflammation; continuously declining PCT levels indicate a better prognosis, even if the peak PCT values are very high.

A persistent increase or failure to decline in the PCT levels has been related to higher mortality rates in various studies [40-43]. On the other hand, as a rule of the thumb, a decline of > 30% per day indicates significant improvement of systemic inflammation. This decline is consistent with the natural plasma disappearance rate of PCT [44].

Local infection

Local bacterial infection or bacterial colonization usually does not induce PCT (for example, tonsillitis, minor soft tissue infection, abscess, local infection of a cerebral ventricular drainage, and even local appendicitis or cholecystitis).

Hence, PCT cannot be used to diagnose (local) infection such as, infection of a cerebral ventricular drainage. In addition, this marker cannot be used as a screening tool to search for infection, if systemic inflammation is not active.

In this situation, however, the patient´s risk of dying from organ dysfunction, sepsis, or severe sepsis is very low. If clinical symptoms indicate a possible sepsis, but the PCT level is low, sepsis therapy should be started anyway, and PCT measurements should be repeated (after 12, 24, 36 hr) until the final diagnosis is clear.

PCT elevation in patients without sepsis

PCT levels may be elevated in patients who do not have sepsis. Plasma levels in these cases usually are not very high (<2 ng/mL), but they may increase significantly in certain conditions, e.g. following liver transplantation, during severe and prolonged cardiogenic shock, in patients with heat shock, severe pancreatitis, and rhabdomyolysis (>2-10 ng/mL).

In addition, certain types of autoimmune disorders may induce significant amounts of PCT. Therefore, it is important that the physician, especially in the ICU, is aware of any such conditions because the sensitivity and specificity of diagnostic tests can be increased, if individual conditions of the patients are taken into account. A selection of conditions where PCT is induced independent of sepsis and infection are indicated in Table 1.

In patients with low PCT levels, antibiotic therapy should be discontinued, if damage from any putative site of infection is not expected. Whether antibiotic therapy should be withheld in neutropenic patients with

fever and normal PCT levels, and in patients with acute pancreatitis and low PCT levels is still under discussion. A low PCT level in patients with acute pancreatitis indicates that antibiotic therapy may not be required, since low PCT levels are associated with a low risk or low severity group of patients, most likely having edematous pancreatitis.

It is yet to be investigated whether PCT is an indicator of urgency for surgery in patients with minor abdominal complaints (e.g. suspected appendicitis), despite several discussions for a possible need for categorization of these patients in order to differentiate complicated cases for urgent intervention and less severe cases only requiring conservative therapy [45-50].

Individual, patient-adapted antibiotic therapy using PCT: "antibiotic stewardship"

PCT-guided antibiotic therapy has been investigated in various studies, which suggest that the duration of antibiotic therapy and unnecessary treatment courses can be avoided and consumption of antibiotics significantly reduced using PCT.

Hence, a PCT-guided approach should be a part of any antibiotic stewardship program to avoid overuse of antibiotics. Meanwhile, as a guide for antibiotic therapy, PCT is also mentioned in various guidelines [10, 11].

Indications

A PCT-guided approach can be used in various patients and indications, but the goal and approach may be different: i) In outpatients, unnecessary antibiotic prescriptions can be avoided because usually the main reason for prescription of antibiotics is reduction of symptoms that may actually be caused by local bacterial or viral infection.

This has been demonstrated specifically for acute respiratory tract infection and exacerbation of COPD [8, 9]. The rate of sepsis and severe infection in these patients is rare and the low cut-off for PCT (e.g. <0.25

ng/mL) provides a level of security due to the high negative predictive value of low concentrations to exclude sepsis. ii).

In critically ill patients with sepsis, severe sepsis, or severe bacterial infections like pneumonia, success of therapy and duration of antibiotic treatment can be evaluated and individually adapted by PCT measurement. Nowadays, individually adapted treatment courses should be the choice, instead of prescribing a fixed term of antibiotics.

Unfortunately, most guidelines still cover only the worst case scenario and hence favor overtreatment. iii) In the ED, diagnosis or confirmation of diagnosis of sepsis or the differential diagnosis is the main indication for PCT measurement.

High PCT levels indicate a high urgency for sepsis therapy, including a search for a focus or surgical intervention. The idea of this concept is that patients with very low or normal PCT levels have a low risk for sepsis and systemic inflammation and hence a low mortality due to severe bacterial infection, at least at the time when low PCT is measured.

Therefore, antibiotic therapy may not be required immediately and after focus removal, successful treatment courses may be discontinued based on the individual patient requirements. Further, only periods of invasive bacterial infection should be treated, rather than colonization or local superinfection.

Also, attempts of eradication of certain strains of microorganisms may have limited success and cause further selection of resistance to the microorganisms. Therefore, such attempts have limited advantage for the patient in the long term.

Exclusion criteria for the use of this concept are situations where PCT is not induced or treatment is required anyway, for example, i) in patients who have no significant PCT response, ii) patients in whom treatment of local infection is essential, e.g. those who have infection of vital organs (e.g. endocarditis, ventriculitis), iii) infection with slowly growing microorganism or tissue, toxin-producing microorganism or infections with low immunogenic responses (like osteomyelitis, tuberculosis, infection with atypical microbe, and sometimes, fungal infection), iv) patients who have severe immunosuppression or a limited ability to eliminate residual infection, and v) patients in whom the focus of infection has not been eliminated.

It is not essential to mention here that an unexpected deterioration of the disease cannot be predicted even by PCT.

Practical approach

As demonstrated in various studies, by using PCT measurements, approximately two to three days of antibiotic consumption can be saved. For a practical approach, we recommend a daily PCT measurement in all critically ill patients from the onset of antibiotic prescription, with the following periods of interpretation: first, during day-2 to day-3 of treatment, success of therapy can be evaluated by assessing the PCT kinetic (e.g. a decline indicates a positive response to therapy).

Condition	Comments /Peak	Expected range	Reference
Surgery, trauma, burn, and inhalation trauma. Surgery/ trauma, thoracic surgery	Maximum values on day 1, rapidly declining CRP peak day 2 or 3, slow decline (1-2 weeks)	<0.5-1 ng/mL for peripheral, non-abdominal trauma or minor abdominal surgery) <2 ng/mL for abdominal surgery or trauma, cardiac surgery. >2 ng/mL expected in patients with major retroperitoneal or abdominal surgery, liver transplantation	[23, 68, 69] [70, 71] [72-75]

Cardiogenic shock	Initially low, but increasing within 1-3 days, if vasopressor support is required	May be intermediate to high (e.g. >0.5 ng/mL to >10 ng/mL)	[76-78]
MODS, severe SIRS (various etiology: severe viral infection, pancreatitis, heat stroke)	Increases with severity. After injection of proinflammatory cytokines or application of anti-lymphocyte antibodies (attenuated by corticosteroids)	0.5 ng/mL-2 ng/mL, rarely >10 ng/mL	[79, 80] [28, 81, 82]
Pancreatitis, severe	Low PCT indicates less severe or edematous pancreatitis. Infection not likely. High levels are related with severity, organ dysfunction and infected necrosis	<0.2 ng/mL: mild or edematous pancreatitis. Severe pancreatitis: 0.5 ng/mL->10 ng/mL	[37-39, 83]
Autoimmune disorders	Induction depends on the type: No or minor induction in: Rheumatoid arthritis, chronic arthritis, systemic scleroderma, amyloidosis, thyroiditis, psoriasis, inflammatory bowel disease, systemic lupus erythematous. May be elevated in: Kawasaki Syndrome, Good pasture's Syndrome, Anti-neutrophil antibody-positive vasculitis, autoimmune hepatitis or primary sclerosing cholangitis, M. Still	Usually less than 0.3-0.5 ng/mL, in some types significant increase >1 ng/mL-10 ng/mL	[84-90]
Severe renal or liver dysfunction	Chronic and moderate elevation, only at severe dysfunction (dialysis, prior to dialysis, Child C). May decline during hemofiltration and after onset of hemodialysis. Cases with increase reported during acute liver failure	In the lower range, 0.1-2 ng/mL, constant elevation	[44, 91-94] [95, 96]
After prolonged resuscitation, myocardial infarction	Peak Day 1	Only In case of prolonged CPR, levels are related with prognosis after CPR. Very faint increase after myocardial infarction.	[97, 98]
Neonates after birth	Peak Day 1-2	Use adapted reference range	[99-102]
End stage of tumor disease	Slow increase. Para neoplastic induction very rare, always by C-cell carcinoma.	Low (0.5-2 ng/mL)	[103] [104]
Rhabdomyolysis	Acute	May be very high	Individual reports

TABLE I: Indications for PCT measurement other than bacterial or fungal infection

Second, from day-3 to day-6 of treatment, one must be aware that antibiotics can be discontinued in the majority of patients at this time (see PCT guided algorithm). In our hospital, we used the algorithm by Bouadma *et al.* [3].

This algorithm involves both criteria of absolute PCT cut-off values and a kinetic algorithm, for either initiation or termination of antibiotic therapy (Fig. 1). The kinetic algorithm is important for the ICU, since very low cut-off values for PCT used in outpatients and the ED (0.2 ng/mL), are less frequently seen in critically ill patients even after successful focus elimination.

Third, latest at day-7- there should be a general rule to stop antibiotic therapy in all patients, unless specific requirements justify further treatment. However, this decision must be actively discussed within the team and documented in writing. Specific indications like treatment of endocarditis or severe bone infection are excluded from this rule.

Various studies indicate that a maximum duration of treatment of approximately seven days is enough to treat even a severe focus of bacterial infection or sepsis [3, 5, 6, 51, 52].

Possible side effects

This concept has no obvious disadvantages for the patient and no adverse effects if used appropriately. Despite of this, there has been criticism that the statistical power to rule out significant effects on mortality may not be enough and investigations so far have mainly included patients with lower respiratory tract infections [53, 54].

Until now, more than 4,000 patients have been evaluated in randomized controlled trials. In a meta-analysis, Schuetz *et al.* [55] reviewed data of 4,221 patients who have been investigated in 14 trials.

The results showed that 134 out of 2,126 patients in the control groups and 118 out of 2,085 patients in the PCT-guided groups died, thus confirming the non-inferiority of PCT on a statistical level, which was equivalent to exclude an effect of PCT measurement on mortality rate below 8-10%.

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 ng/mL < 1 ng/mL	>= 1 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...

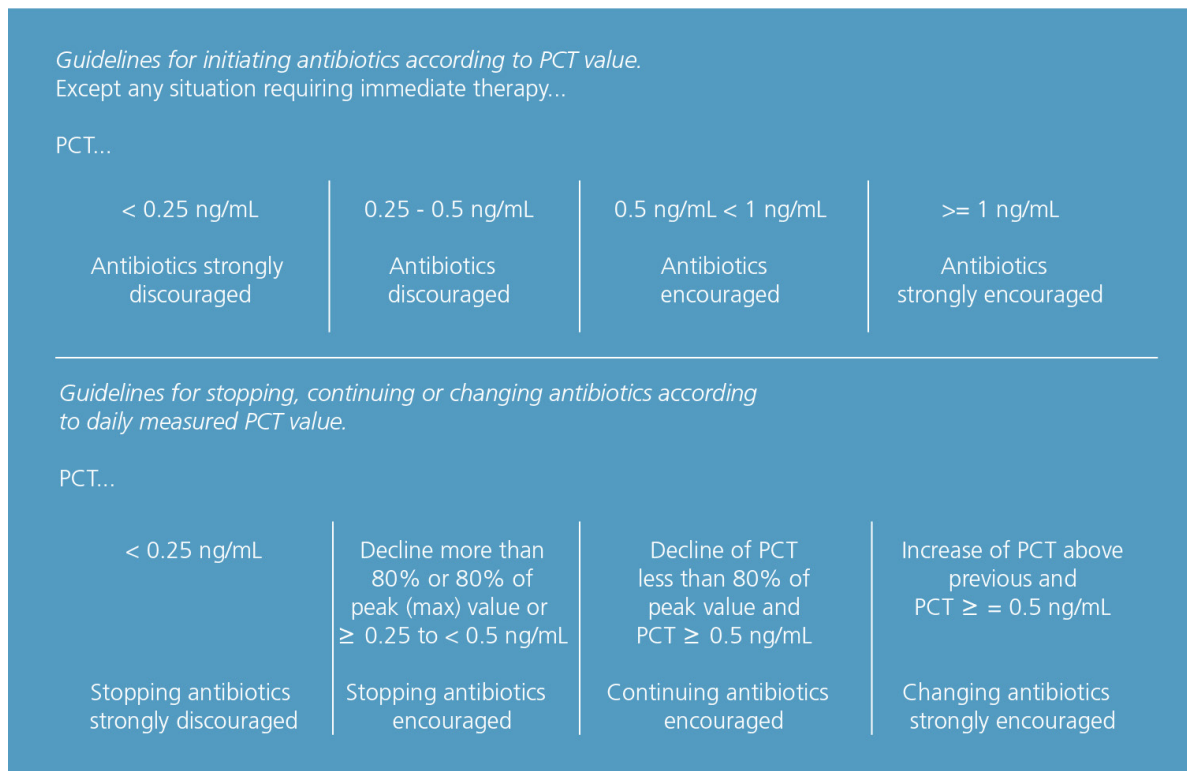| < 0.25 ng/mL	Decline more than 80% or 80% of peak (max) value or ≥ 0.25 to < 0.5 ng/mL	Decline of PCT less than 80% of peak value and PCT ≥ 0.5 ng/mL	Increase of PCT above previous and PCT ≥ = 0.5 ng/mL
Stopping antibiotics strongly discouraged	Stopping antibiotics encouraged	Continuing antibiotics encouraged	Changing antibiotics strongly encouraged

Fig. 1. Example of an algorithm for an individual guide of antibiotic therapy according to Bouadma *et al.* [3].

In a computer-based model, retrospective data analysis from 1,312 ICU patients and an arbitrary use of PCT-algorithm showed substantial reduction in the treatment costs, based on the German DRG system (DRG, diagnosis related groups, a system of disease related reimbursement) [56].

Two minor studies in France did not see a beneficial effect of PCT based algorithm, but others confirmed the significant reduction of antibiotic use in the clinical routine as well [57, 58]. Further studies are under way, e.g. in the Netherlands that includes more than 1,800 patients [59].

However, it is important to consider that the results of such studies always depend on the training and experience of the team, the level of implementation of the method, regional features, and the patients selected [60-62].

Data of previous studies: outpatients and the ED

The group of B. Mueller, M. Briel, and P. Schütz conducted a multi-center trial in outpatients, including 458 patients for whom the treating physician initially decided to prescribe antibiotics on a routine basis, and the control group. In the treatment group, the decision was re-evaluated after presentation of the PCT-guided recommendation (no prescription if PCT <0.1 ng/mL or <0.25 ng/mL).

As a result, 72% of patients in the PCT- guided group did not get antibiotics as compared to the control group. They did not have more complications, the number of sick days was the same, and fewer side effects, such as diarrhea, were observed [8].

In patients with exacerbation of COPD, a similar PCT-guided algorithm was used [9]. In the control group (without PCT measurement), the antibiotic prescription rate was 72%, while in the PCT-guided group it was 40%. During a 6-month follow-up period, complication rates were similar in both groups (regarding mortality, hospitalization, and reinfection). Also, in this study, a low PCT cut-off value for the decision of "no antibiotics recommendation" was used (0.1 to 0.25 ng/mL).

Further studies confirmed feasibility and usefulness of this approach in outpatients and the ED in different circumstances in a higher number of patients.

In another multicenter study, where 1,759 patients were included, duration of antibiotic therapy was 1.5 days shorter in the PCT- guided group (7.4 vs. 5.9 days) [57]. For acute exacerbation of infection in patients with idiopathic pulmonary fibrosis and for treatment of patients with malignancies, reduction in the use of antibiotics with the help of PCT measurement has also been reported [63, 64].

In 243 patients, presenting in the ED with respiratory tract infections and symptoms of dyspnea and cough, prescription of antibiotics was only 44% in the PCT-guided group as compared to 83% in the controls. Primarily, patients with no bacterial infection (asthma) or a non-invasive disease (e.g. bronchitis) did not get antibiotics [65].

1. Community Acquired Pneumonia In patients with community-acquired pneumonia (CAP) (N=302), 151 patients were treated according to the recommendation of a PCT-based algorithm. Duration of antibiotic treatment was 5 days in the PCT- guided group as compared to 12 days in controls.

In patients who had a lower risk or a less severe pneumonia (pneumonia severity index PSI I-III), treatment courses were even shorter (4 days or less). In patients who had severe pneumonia or a high-risk classification (PSI IV-V), treatment courses were not longer than 7 days in the majority of patients [66].

Schuetz et al. [51] analyzed 671 patients in a PCT-guided group and 688 patients as controls. Patients had respiratory tract infections of different types and severity (CAP, eCOPD, and bronchitis).

Exposure to antibiotics was reduced approximately one third in all diagnostic groups, with an overruling rate

of approximately 10% for both predefined criteria and the individual decision of the treating physicians to not obey the recommendation of the algorithm.

Adverse effects were not significantly different in both groups.

In the study by Bouadma et al. [3], 621 patients with different diagnosis were included. This study mainly included patients with lower respiratory tract infections (CAP and ventilator-associated pneumonia [VAP]), but also had some patients with abdominal and urinary tract infections.

Exposure to antibiotics was reduced by 23% in the test group as compared to the control group during the 28-day observation period.

Other diagnosis and patients with sepsis

Even though patients with diagnosis other than pneumonia were underrepresented in these studies, further data indicate that a PCT-guided antibiotic stewardship can be achieved in patients with other diseases as well.

Using a similar PCT-based algorithm, 101 patients with VAP were analyzed and it was observed that the duration of therapy was 9.5 days in the PCT-guided group (51 patients) as compared to 13 days in the control group [4].

In another study, Nobre et al. [52] analyzed 68 patients with severe sepsis out of which, 31 patients were treated according to the recommendations of a PCT-guided algorithm. It was found that the duration of antibiotic treatment course was 3.5 days shorter in the PCT group as compared to the control group.

Hochreiter and Schroeder et al. [5, 6] analyzed postsurgical patients with sepsis and patients with severe sepsis, using another algorithm (PCT cut-off <1 ng/mL or decline of >30% after 3 days) and treatment duration in the PCT-guided group was 5.9 days vs. 7.9 days in control group.

A review of data from 2005 to 2009 (when the PCT-guided algorithm was introduced), indicated reduction in the duration of antibiotic courses from 14 days in 2005 to 9 days in 2009 [67].

In 71 patients with severe acute pancreatitis, a PCT-guided approach (cut-off >0.5 ng/mL, semi-quantitative assay) resulted in reduced antibiotic therapy and shorter duration of hospitalization [7].

Guidelines

Most currently used guidelines are not able to clearly stratify patients according to their individual response to therapy, because most of the guidelines provide recommendations for a maximum duration of antibiotic therapy only in order to cover the worst-case scenario, which could result due to medico-legal reasons and non-availability of good documentable criteria for the progress of source control and treatment of systemic inflammation.

However, some recent guidelines have changed and addressed PCT-guided algorithm. For example, the updated pneumonia guideline and the sepsis guideline in Germany recommend individually adapted treatment course using PCT for diagnosis and treatment [10, 11].

In addition, the Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, published in 2012, indicate that PCT can be used for the diagnosis of sepsis and to terminate antibiotic therapy in patients who initially appeared septic, but have no subsequent evidence of infection [2].

Hence, it is expected that in future further guidelines will address the individual treatment requirements rather than a fixed treatment course with antibiotics.

Summary

Daily quantitative measurement of PCT is recommended in the ICU for all critically ill patients with a suggested diagnosis of systemic inflammation, after focus removal, and immediately after onset of antibiotic therapy to

monitor systemic inflammation and success of therapy.

This approach affects therapeutic and diagnostic decisions and limits the duration of antibiotic therapy, if plasma PCT levels are interpreted together with clinical signs and conventional diagnostic methods.

Further indications for PCT measurement are based on PCT induction in specific conditions, such as, bacterial sepsis, meningitis, assessment of the presence or severity of systemic inflammation, and requirement of antibiotic therapy.

In addition, PCT measurement can also be used as a tool to exclude severe systemic inflammation in patients in whom local infection or bacterial colonization is seen.

PCT can be used to guide antibiotic therapy not only in patients with lower respiratory tract infections and pneumonia, but also in patients with sepsis or severe sepsis of different source, resulting in a more rational use of antibiotics.

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