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Laboratory parameters for the diagnosis and management of infections in an intensive care setting

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Summary

Even today diagnosing infections and sepsis in a rapid and reliable fashion remains a crucial challenge in modern intensive care medicine. Both the Surviving Sepsis Campaign and the current German S3 guidelines assign a central role to early diagnosis and treatment of sepsis. The lack of any causal therapy makes timely antibiotic treatment, in addition to source control, a major factor in improving a patient's prognosis and probability of survival [1]. As such, correctly diagnosing infections and subsequently guiding (commencing, dosing, discontinuing) appropriate anti-infective treatment remain game-changing challenges, especially in an intensive care setting. Investigations have been undertaken in the last number of years to determine the diagnostic value of conventional markers of infection and inflammation such as C-reactive protein, leucocyte count and serum procalcitonin, and their suitability for guiding treatment [2,3]. That's in addition to an almost insurmountable number of promising new "infection biomarkers" such as interleukin-6 [3]. A comprehensive review of sepsis biomarkers published as far back as 2010 listed more than 170 different parameters which might show potential in diagnosing infections or guiding anti-infective treatment [3]. Furthermore, multimodal or multiparameter approaches [4], but also more sophisticated evaluations of conventional parameters such as the neutrophil-to-lymphocyte ratio [5] may have their own potential. However, most of these parameters have not come to be a part of everyday clinical routine and will therefore not be discussed here in any detail. Focusing on an intensive care setting, this article aims to provide a practical overview of routinely utilised infection biomarkers, detailing their potential applications and limitations.

Introduction

In addition to the usually decisive clinical signs and symptoms, the gold standard for diagnosing infections remains the isolation of pathogens from cultures obtained from the assumed focus and/or blood. At between 1 to 5 days, the time to positivity for cultures remains an important and inherent limitation.

Despite their generally limited specificity, the importance of clinical signs and symptoms of infection (e.g., fever, chills, lethargy, confusion, tachycardia, hypotension, and tachypnoea) in everyday clinical practice should not be underestimated. They generally represent the basis for suspecting infection. Altered body temperature (pyrexia or hypothermia) is one of the cardinal signs of infection and the notable significance is highlighted in the current S3 guidelines on sepsis [6].

Microbiologic staining (such as the Gram stain) is a simple and cost-effective method which is unfortunately little regarded in everyday clinical practice. However, it can be useful, especially so when samples have been attained from a primarily sterile medium (such as cerebrospinal fluid), providing a rapid (<1 hour) preliminary identification of possible pathogens.

Irrespective of these methods, a biomarker providing simple and rapid evidence of infection would be highly welcome. In an ideal situation, the patient's blood would be analysed quickly (<1 hour), providing highly sensitive and highly specific evidence of infection. Again, ideally, the results would allow inference of the causative pathogens.

This **ideal biomarker of infection** should fulfil the following requirements with high specificity and sensitivity (>90 % respectively):

- Recognise infection at an early stage
- Differentiate between infectious and non-infectious aetiologies
- Differentiate between bacterial, viral, fungal, and parasitic disease
- Predict the patient prognosis
- Provide information on the response to treatment in the course of the disease, potentially aiding in modulating treatment
- Show a safe point for discontinuation of anti-infective treatment
- Provide valid statements on the course of the disease through a clinically useful half-life
- Be easily tested, reproducible and unsusceptible to confounding factors
- Be cheap, but easy to quantify.

None of the currently available biomarkers can be described as optimal or ideal with regard to the points described above. This is one reason for the impressive increase in the number of new (but equally suboptimal) biomarkers. Despite their differing characteristics, the **leucocyte count** (white blood cells, WBC), **C-reactive protein**, the slightly newer **interleukin-6** (IL-6) and **procalcitonin** (PCT) have become established as the biomarkers of infection in everyday clinical practice, each with its own strengths and weaknesses. CRP – an acute phase protein – and the WBC, for example, provide sensitive detection of inflammation but exhibit a very low specificity for infectious processes, implying a high rate of false positives. In contrast procalcitonin, for example, exhibits a more favourable specificity for identifying bacterial infections. Despite all their limitations detailed throughout this text, these biomarkers can aid in diagnosing infections and making treatment decisions (Table 1). As such, PCT, for example, takes on a corresponding role in both the current sepsis guidelines and guidelines on the treatment of community acquired pneumonia in adults [6,7].

It should be reiterated that all biomarkers currently used for diagnosing infections and managing treatment **do not exhibit sufficient sensitivity and specificity** (e.g., compared to troponin in myocardial infarction) and that as such, decisions cannot be based on a biomarker alone. They all display a **level of uncertainty** (i.e., they are imperfect biomarkers) that means that they should only be **used in synopsis with clinical signs and symptoms**.

The use of imperfect biomarkers with their respective limitations (suboptimal sensitivity and specificity) requires that they be implemented in a clinical context. As such, the diagnosis and management of treatment should not be based solely on an altered biomarker but must instead incorporate a detailed medical history and complete objective clinical examination.

Imperfect biomarkers with a sensitivity and specificity below 90 % can still aid us in reducing the number of estimation and decision errors made in everyday clinical practice. This is especially true of situations in which safe decisions cannot be taken based on a clinical examination and medical history alone. In these situations, the addition of an imperfect biomarker can aid in steering the decision in the right direction as illustrated in Figure 1.

The decisions outlined in Figure 1 focus mainly on two clinically relevant questions:

Table 1
Biomarkers routinely used for diagnosing infections and managing treatment in a clinical setting.

	Specificity for infection	Sensitivity for infection	Clinical use	
			Advantages	Disadvantages
Leucocytes	-	+	Inexpensive, good sensitivity	Insufficient specificity (variance often not associated with infection)
C-reactive protein	-	++	Inexpensive, high sensitivity	Insufficient correlation with severity Insufficient specificity (non-infectious increase)
Procalcitonin	+++	+/-	High specificity for bacterial infections Correlates well with severity Rapid induction (<12 h) High biostability	Poor value in some types of infection (e.g., neutropenia or endocarditis) No inference of source of infection Cost-intensive
Interleukin-6	+/-	+++	Sufficient correlation with severity Very good sensitivity Very rapid induction	Very short half-life/low biostability High costs

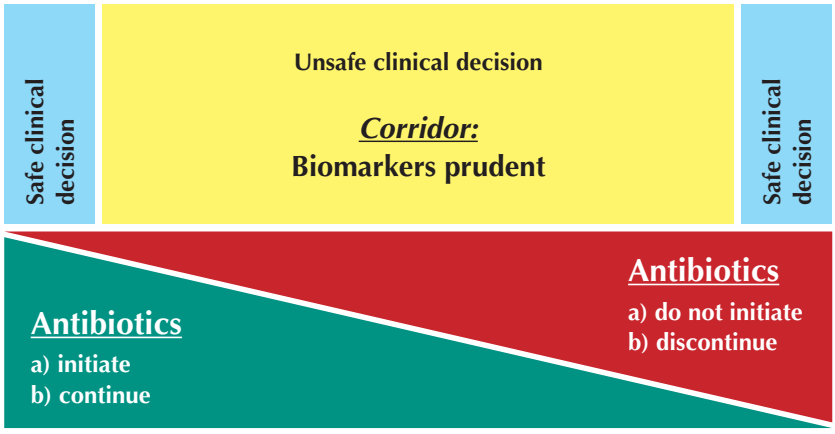
1. Is infection present – should anti-infective treatment be initiated?
2. Has the infection been treated with anti-infectives for a sufficient length of time – can antibiotic treatment be discontinued?

For each of the four biomarkers (WBC, CRP, PCT, IL-6), both of these questions are presented in a structured manner and discussed below based on current literature.

Leucocytes

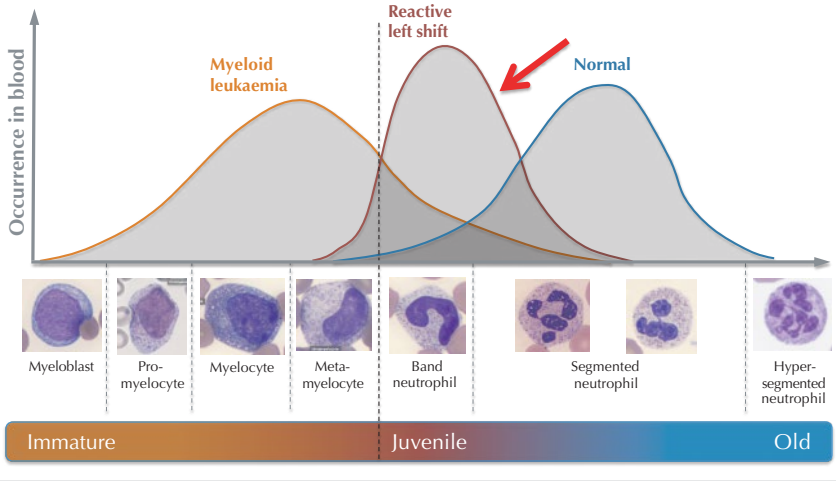
White blood cells are providers of non-specific (granulocytes, monocytes) and specific (lymphocytes) immune defences. In general, acute infections often exhibit a **neutrophilic initiation phase** followed by a **monocytic defence phase** and a **lymphocytic-eosinophilic healing phase**. Bacterial infection especially displays an initial increase in the total number of neutrophils (so-called neutrophilia), with the proportion of juvenile neutrophils increasing at the same time. Usually, the **juvenile form** (band neutrophils) makes up approximately 3–5 % of the total number of neutrophils. A significantly higher proportion of band neutrophils can suggest bacterial infection but can also be associated with non-infectious inflammation or stress [8]. These changes are termed a **reactive left shift** (Figure 2). This change needs to be differentiated from a pathological left shift, which is usually associated with myeloid leukaemia and characterised by the increased presence of immature forms (e.g., myeloblasts or myelocytes) (Figure 2).

Figure 1



Scheme of clinical decision making. The blue areas to the left and to the right represent situations in which a safe decision can be derived based on the clinical situation alone and use of a biomarker would convey no additional benefit. The yellow middle section represents situations in which safe decisions cannot be based on clinical parameters alone. In these situations available biomarkers may provide relevant additional benefits.

Figure 2



Granulocyte maturation stages. Left shift in infection or acute inflammation (**red arrow**), with an increased number of juvenile (band) neutrophils in the blood.

Images sourced from the American Society of Hematology Image Bank (http://imagebank.hematology.org).

The production of neutrophils is significantly upregulated in the presence of bacterial infection in particular, with neutrophils dominating the differential blood count. In contrast, viral infection is often characterised by an increase in the proportion of lymphocytes rather than an increased number of neutrophils.

In consequence, the **neutrophil-to-lymphocyte-ratio** (NLCR) has become established as a marker of infection beside the generally helpful determination of a left shift. The probability of bacterial infection increases with a high NLCR, whilst a low NLCR is associated with increased probability of viral infection. In a recent paper, a cut-off value of 6.2 for the NLCR was able to predict bacterial infection with a sensitivity of 91 % and a specificity of 96 % [9]. The corollary for clinical practice is that for NLCR < 6 the possibility of viral infection should be evaluated, whilst for NLCR > 6 viral infection is less likely. Furthermore the NLCR seems to be a suitable predictor of bacteraemia. Loonen [10] was able to show that an NLCR ≥ 10 predicted bacteraemia with a sensitivity of 85 % and a specificity of 51 %.

Regardless of the NLCR, a more detailed take on the differential blood count is typically quite informative. **Secondary**

occurrence of lymphopenia (≤0.9 x 10^3 lymphocytes/µl) following an initial hyper-inflammatory phase particularly in an intensive care environment, for example, seems to be an important risk factor for ICU associated opportunistic infections. These patients show a markedly increased probability of virus reactivation (of, for example, CMV or the herpes virus) and fungal infections [11]. Notable shifts within the granulocyte populations can also be valuable when considering differential diagnoses. A notable increase in the number of eosinophils (eosinophilia), for example, suggests that an allergic reaction should be considered as a possible cause of an inflammatory reaction, whilst basophilia might point to a parasitic infection. In situations in which the condition of patients already under broad antibiotic treatment regresses, the differential blood count can therefore help identify causes which might otherwise be missed.

It remains the case that the sensitivity and specificity of the WBC are generally unsuited to diagnosing infections and managing treatment. As such, irrespective of the helpful details above, the leucocyte count has lost its significance, especially in situations in which PCT is routinely measured. Despite this, the leucocyte and differential blood count should be included in the evaluation of a patient, especially as they are typically part of the laboratory workup in cases of severe infection.

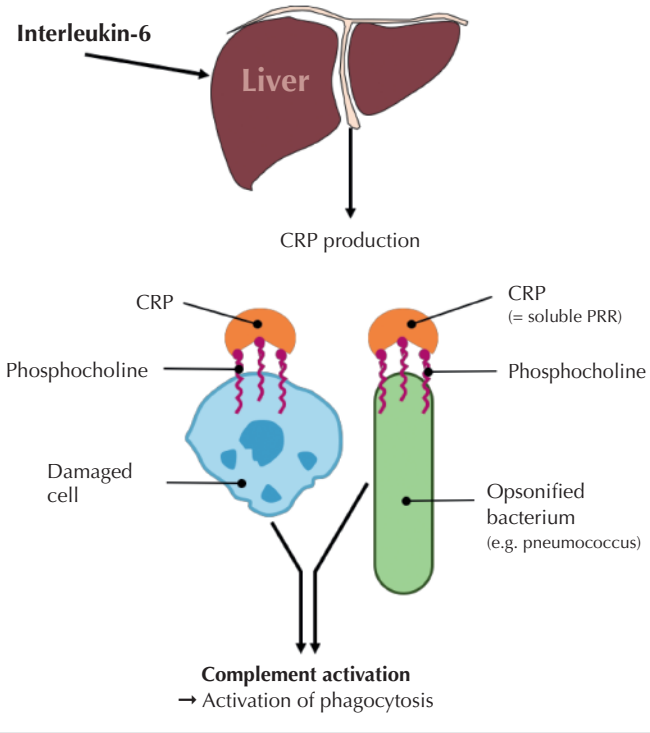
A differential blood count should be ordered when evaluating infections. In addition to showing a reactive left shift and aiding in risk stratification with regard to viral and fungal infections, the differential blood count can point to other causes of inflammation such as allergic reactions or parasitic infections for consideration as differential diagnoses.

C-reactive protein (CRP)

CRP was the first acute phase protein to be described. It was named after its ability to precipitate the C-polysaccharide of pneumococcus when it was first described as a test for pneumococcal pneumonia in 1930. CRP is synthesised in and released from hepatocytes mainly through stimulation of interleukin-6. As such, CRP is highly sensitive for systemic inflammation and tissue damage. It is produced approximately 4–6 hours after the causative stimulus (e.g., the start of an infection). It doubles its concentration in blood within 8 hours and reaches a peak after 36–50 hours [12]. The reference value for plasma CRP is <1 mg/dl; in severe infections values of up to and above 50 mg/dl may be reached. Due to polymorphisms (e.g., in the CRP-gene itself), significant inter-individual differences are to be expected in CRP levels, however, such that the concentration does not sufficiently correlate with disease severity [3].

CRP belongs to the group of pentraxins, a highly conserved family of pentameric proteins [13]. Above all its biological role is to activate the complement system and other inflammatory processes [14]. One of its significant functions is to act as a soluble pathogen recognition receptor (PRR), binding in particular to phosphocholine on bacterial cell walls, but also to phosphocholine in the cell membranes of damaged cells. Host phosphocholine from damaged cells is detected by the immune system, making cells infected by viruses or damaged by mechanisms other than infection points of attack for CRP. Binding of CRP to phosphocholine (so-called opsonisation) mediates complement activation, inducing phagocytosis triggered by the Fc receptor (Figure 3). As such, CRP not only mediates inflammation but is actively involved in eliminating pathogens [13,14]. Amongst other things, a lack of CRP manifests itself in a significantly increased susceptibility to pneumococcal infections as was shown, for example, using CRP-knockout mice [15]. CRP, then, has a key role in acute inflammatory reactions and is extensively involved in immune cascades. It remains to be said, however, that increased levels of CRP are unspecific, so may be associated with non-infectious disease through

Figure 3



Simplified scheme showing the release and action of C-reactive protein (CRP) and its function as a pathogen recognition receptor (PRR).

interaction with damaged cells connected with autoimmune disease, acute coronary syndrome, reperfusion injury, rheumatic disease, malignant tumours or following trauma or surgical interventions [16].

In everyday clinical practice, CRP is probably the most commonly used biomarker to determine the presence and severity of an infection. Its popularity can be explained by the introduction of highly sensitive, automated testing and the moderate cost of testing when compared with other available markers. As mentioned, however, CRP levels are raised in a whole number of non-infectious conditions, such that the specificity of this biomarker is low. As such, it would seem problematic to base decisions on antibiotic treatment on a raised CRP level. Additionally, whilst CRP levels increase rapidly, in comparison with cytokines (e.g., IL-6) or PCT, they don't reach their maximum until a late stage (after more than 24 hours) (Figure 4) [17]. This means that CRP levels remain raised over a period of several days even when the focus of infection has already been cleared and no formal treatment indication remains [17].

The value of CRP in diagnosing acute infections in critically ill patients is controversial [18]. The sensitivity and specificity of CRP in diagnosing infections varies significantly between studies [18].

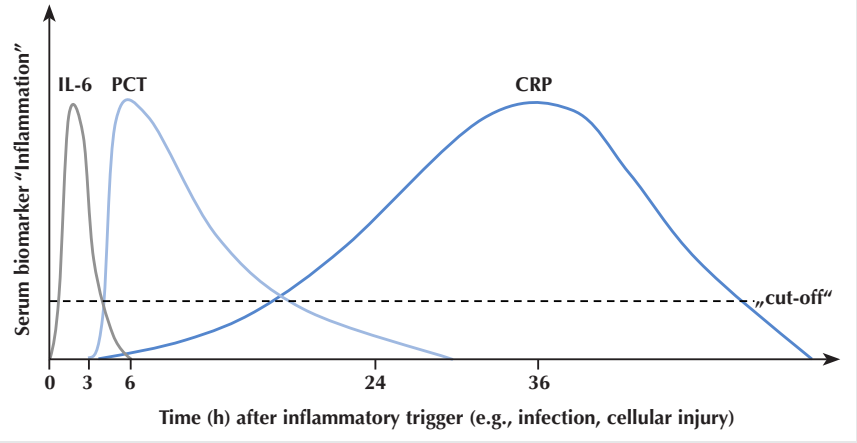
In summary, CRP values do not permit safe differentiation between sepsis or severe infection and systemic inflammation of a non-infectious origin or acute organ damage. This potentially limits the suitability of CRP as a biomarker for infection.

Despite the limitations set out above, numerous studies have shown that in a clinical setting determining CRP supports evaluation of the severity of an infection or the extent of inflammation [19] and judging patient prognosis [20]. Furthermore, a Cochrane Review showed a reduction in the prescription of antibiotics in a non-intensive care setting when a CRP algorithm was employed [21]. And in an intensive care setting, single studies have shown that CRP can be utilised to meaningfully support diagnostics and the management of treatment [22,23]. All in all, it should be said that there is currently no evidence to show that CRP is inferior to other biomarkers. In this context, in the current prospective CAPTAIN study, CRP is shown to be non-inferior to all other biomarkers when used to discriminate between (non-infectious) SIRS and sepsis [24]. **Changing trends in CRP kinetics** in particular seem to have a high diagnostic accuracy [25]. As such, a renewed increase in CRP levels from the 3rd post-operative day on or following (assumed) eradication of the septic focus may indicate an acute (and often infectious) problem, although important non-infectious differential diagnoses also need to be weighed [26]. Stagnating CRP levels or renewed increases of an infectious aetiology may be associated with **surgical complications** (e.g., abscess formation, anastomotic insufficiency, etc.) or **insufficient antibiotic therapy**. Consequently, CRP can be of significant value in detecting relevant (infectious and non-infectious) post-operative complications and possibly in managing treatment. In addition, combining CRP with clinical signs such as fever, tachycardia, and tachypnoea seems to increase the specificity for diagnosing infectious disease to a relevant degree [18]. The theoretical principles of CRP diagnostics detailed above are supported by the following case vignette.

Case vignette: isolated postoperative increase in CRP levels

After an initially inconspicuous course following laparoscopic sigmoidectomy, a 50-year-old patient showed fever, increased dyspnoea, and increasing haemodynamic instability as well as an isolated increase in CRP from 6 mg/dl the previous day to 48 mg/dl (PCT and leucocytes remained unchanged). In this scenario the question of possible differential causes of increasing CRP levels comes immediately to mind. As a first step, we can determine that the increase is clinically relevant, because it is associated with an objective regression in the patient's condition. An increased CRP level can have a number of infectious causes (e.g., catheter associated infections, abscess formation, wound infections, anastomotic insufficiency, fungal infections). However, evaluation of differential diagnoses provided no evidence of an acute infectious problem. As rising CRP levels are not specific to infections, other non-infectious causes such as pulmonary embolism must be considered.

Figure 4



Schematic representation of the kinetics of various biomarkers: C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT).

Computed tomography pulmonary angiography was performed and demonstrated a significant occlusion in the right pulmonary arterial tree, which had caused both the increase in CRP and the clinical signs and symptoms.

CRP is the most commonly used biomarker to detect an inflammatory response. Individual, isolated CRP values play a lesser role as a specific marker of infection or sepsis in intensive care. Changes in trends of CRP levels and the combination with clinical signs and symptoms of infection seem to increase the diagnostic accuracy significantly. Despite the inadequate specificity of CRP, current literature does not show it to be primarily inferior to other biomarkers. Especially in the case of an isolated increase in CRP, however, non-infectious aetiologies should be considered in the differential diagnoses.

Procalcitonin (PCT)

PCT is a polypeptide made up of 116 amino acids and is the precursor for the hormone calcitonin. Whilst calcitonin exerts relevant influence on the regulation of calcium metabolism, PCT itself does not have any calcium regulating properties. Under normal conditions relevant quantities of PCT are only produced in neuroendocrine C-cells of the thyroid gland whilst production in other cells is suppressed. Subsequently, PCT is enzymatically cleaved within the C-cells of the thyroid gland into calcitonin and stored in secretory granules. In the context of an infection, repression of the calcitonin gene is lifted and PCT production subsequently also occurs in parenchymatous organs such as the liver, kidneys, fatty tissue, and other differentiated cells within the body. PCT produced this way is secreted into the bloodstream, leading to a rapid increase in PCT concentration in blood, reaching levels many times higher than the reference value. Extrathyroidal PCT does not undergo cleaving (to calcitonin), so that it has no relevant effect on calcium metabolism.

Determining PCT levels requires only a few millilitres of serum or of heparin or EDTA plasma. Samples are stable for a number of hours at room temperature (although most labs recommend transport times of less than 4 hours). PCT levels can be determined without difficulty from refrigerated samples (4 °C) even after a number of days. As such, this biomarker ticks many of the boxes for widespread use in hospitals. However, the technical prerequisites for the test are relatively complex and testing costs are not inexpensive, so that PCT testing is not routinely available in all hospitals.

PCT levels in blood increase in the context of bacterial infections in particular, and at the same time correlate with the severity and lethality. It is interesting to note that in the context of viral infections PCT production is suppressed by interferon gamma, making PCT a relatively specific diagnostic and prognostic marker for bacterial infections. A further advantage of PCT when compared with CRP is that the former is not influenced by treatment with corticosteroids. These factors explain the higher specificity of PCT for bacterial infections when compared with the other available biomarkers. The significance of PCT for diagnosing infections is not uniform across infections, however. Table 2 presents an overview of current evidence on procalcitonin in various clinical situations or for various infections.

The potentially greatest clinical benefit of PCT is that this biomarker can be used to support an earlier and objective decision on initiating and discontinuing antibiotic treatment. A clinical response to an antibiotic will lead to a rapid decrease in PCT levels, making PCT an interesting marker for antibiotic management. Whilst guidelines often suggest a fixed duration for antibiotic treatment, management using PCT levels means that treatment durations can be individually tailored to the patient's response. This is especially helpful when

Table 2
Overview of current evidence relating to PCT algorithms for diagnosing infections (based on [27]).

Type of infection	Use	PCT cut-off (µg/l)	Evidence
Pneumonia	Severity and indication for antibiotic treatment	0,25–0,5	+++
Sepsis/septic shock	Sepsis vs. SIRS	0,5–1,0	+++
Meningitis	Determining infectious aetiology	0,5	+++
Upper airway infection	Viral vs. bacterial	0,1	+++
Acute bronchitis	Rationale for antibiotic treatment	0,1–0,25	++
Exacerbated COPD	Triggered by infection	0,1–0,25	++
Abdominal infections	Excluding necrosis / ischaemia	0,25	++
Urinary tract infections	Severity and indication for antibiotic treatment	0,25	++
Bloodstream infections	Differentiating between bacteraemia and contamination	0,1–0,25	++
Postoperative infections	Especially when value fails to decrease or with secondary increase	kinetics	+/++
Endocarditis	Suspected acute infectious endocarditis	> 2,0	+
Appendicitis	%	0,25	+
Arthritis	Differentiating between septic vs. non-infectious arthritis	0,1–0,25	+
Neutropenia	Estimating risk of bacterial infection	?	-

providing antibiotic treatment in an intensive care environment. A reliable way of avoiding unnecessary antibiotic treatment with associated side effects and the development of resistance, and of reducing the treatment duration has long been sought. A randomised study showed that the duration of antibiotic treatment of patients with community acquired pneumonia could be reduced from 13 to 6 days using a PCT guided algorithm, without compromising the outcome [28]. The ProHOSP study confirmed these results in 2009 [29]: patients with lower respiratory tract infections in the PCT guided treatment arm showed a significant reduction in antibiotic use and associated side effects whilst treatment success was unaffected [29]. The results from the ProREAL study [30] which followed on from the ProHOSP study are especially interesting: data showed that both a physician's training status and experience are decisive factors in effectively and successfully deploying a PCT algorithm in a hospital. Investigators were still able to observe the positive effect of training in the participating centres after a latency of one year.

Obviously there are limits to such **de-escalation algorithms**, as was recently shown in an article published in the New England Journal of Medicine [31]. The authors once again investigated the influence of PCT algorithms on the duration of antibiotic treatment for lower respiratory tract infections. In contrast to the numerous other studies showing a positive effect, this investigation was not able to show a reduction in the duration of antibiotic treatment mediated by PCT algorithms. At first glance, this contradiction of previous investigations might seem surprising. However, as is so often the case, the explanation is to be found in the details. Correct interpretation of the findings requires that the short average duration of antibiotic treatment of the underlying pneumonia in the control group – a rather impressive 4 days [31] – be taken into account. In conclusion, what was shown was that determining PCT is not essential if excellent antibiotic stewardship (ABS) – which can facilitate very early discontinuation of antibiotic treatment even without biomarker support – has been established.

Randomised studies have also provided evidence for PCT directed management of antibiotic therapy in patients treated for sepsis on intensive care units. A study by De Jong et al. in 2016 in particular showed that PCT directed antibiotic treatment resulted in a reduced duration of treatment. In consequence, antibiotic use was reduced, a fact which was associated with increased survival [32]. The randomised, controlled investigation included 4,507 patients on various intensive care units in the Netherlands. The intervention group was treated based on a PCT algorithm, whilst the control group was treated in accordance with local antibiotic guidelines. In PCT directed treatment, antibiotics were discontinued once PCT levels dropped to ≤0.5 µg/l or following a decrease of ≥80 % of the maximum value. This algorithm resulted in reduced antibiotic use and at the same time reduced the mortality rate by approximately 25 %. Since then, numerous meta-analyses have analysed these effects across studies on intensive care patients. They, too, have shown a **significant reduction in the duration of antibiotic treatment**, and in some cases an influence of PCT measurements and algorithms on mortality [33,34]. It should be noted, however, that these advantages – especially with regard to mortality – were not unreservedly established by all investigations [35]. This is largely due to differing PCT decision algorithms. A meta-analysis recently published in Chest provided some clarity, at least temporarily [33]. The investigation was distinctive for its inclusion of previously neglected confounders (such as the use of antibiotic stewardship programs, concurrent use of other biomarkers such as CRP, adherence to the study protocol) in the statistical analysis. Once again, this meta-analysis was able to convincingly demonstrate that PCT directed decisions aid in de-escalation of antibiotic therapy in critically ill patients. Even if it was also able to confirm a survival benefit though use of PCT algorithms, it should be noted that in this regard the grade of evidence was weak. Regardless, the rising rate of multiresistent pathogens and Clostridioides difficile infections worldwide taken together with the currently dry antibiotic pipeline mandate avoiding inappropriate and undue antibiotic use. It may be assumed that use of PCT algorithms reduces excessive antibiotic use. Numerous investigations have also shown a reduction in side effects, and in some cases an associated improvement in patient outcome; this is especially true when repeat PCT measurements are employed. The premise, of course, is an in-depth knowledge of the strengths and weaknesses of this biomarker and prudent implementation in clinical routines or ABS programs.

When employing PCT algorithms in intensive care, the right use and correct interpretation of the PCT values seems to be crucial. A positive effect on mortality and a reduction in the duration of antibiotic therapy were observed above all when PCT was repeatedly determined and used especially for discontinuing antibiotic therapy. It is this strength – i.e., early discontinuation of antibiotic therapy – to which the extensive body of literature lends PCT a central role in intensive care.

Despite this, PCT directed treatment has specific limitations in everyday clinical practice. PCT values can be raised in non-infectious situations such as in the presence of tumours (e.g. ectopic production in bronchial carcinoma), following major surgery or in the context of burns. Low PCT values are seen despite infection especially in the case of mild respiratory infections with **atypical pathogens** (e.g. mycoplasma or chlamydia) or in strictly localised or subacute infections (abscess or pleural empyema, or endocarditis). **Renal failure** with decreased clearance is another relevant confounding factor when interpreting raised PCT levels. Decreased renal elimination leads to higher plasma levels, with glomerular filtration rates (GFR) below 30 ml/min leading to an increase in half-life from 24 to 40 hours. In con-

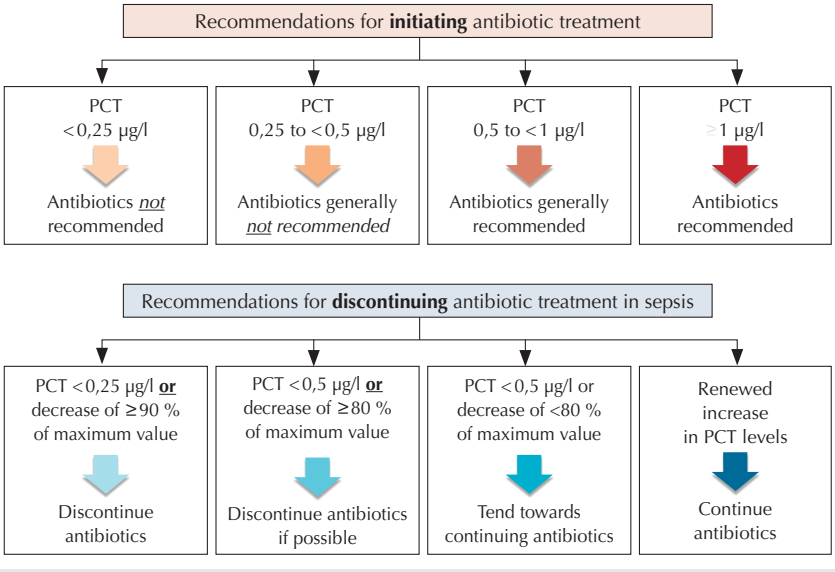
trast, **extracorporeal renal replacement** leads to an artificial decrease in PCT levels through filtration and absorption by the dialysis filter/membrane. This may lead to PCT being unsuitable for diagnosing bacterial infection in patients undergoing haemodialysis for renal failure [37]. Overall it should be noted that procalcitonin should be interpreted in conjunction with a detailed medical history and precise clinical examination.

Case vignette: discontinuing antibiotic treatment for pneumonia

A 75-year-old patient with a history of COPD is brought to casualty by paramedics, complaining of fever, dyspnoea, productive cough, and malaise. A positive quickSOFA score led to a diagnosis of sepsis, and the patient was moved to intensive care immediately. Pneumonia was confirmed as the focus of infection on chest radiography and sputum diagnostics. Once blood had been drawn for culture, empiric antibiotic treatment was commenced with piperacillin and tazobactam (+ macrolide for 3 days). Initial labs showed a serum PCT of 6 µg/l. Complete remission was achieved after 6 days, and PCT dropped to 0.56 µg/l. The question at this point was whether antibiotic therapy could be discontinued. A PCT algorithm (see Figure 5) can be helpful in such cases. With a decrease in PCT levels of ≥ 90 % of the maximum (6 µg/l to 0.56 µg/l) the decision can be taken to discontinue antibiotic therapy.

Initial PCT levels can also provide a certain basis for **determining patient prognosis**. If after the first 1–2 days of antibiotic therapy no decrease in PCT levels is observed then treatment failure should be considered, especially when seen in conjunction with a regression of the patient's clinical condition. In these cases, the diagnosis should be re-evaluated and the choice of antibiotic potentially modified. In short, numerous helpful pieces of information which meaningfully support clinical decision making can be inferred from PCT values.

Figure 5



Procalcitonin (PCT) algorithm for initiating and discontinuing antibiotic treatment in sepsis on the intensive care unit (based on [32]). Daily PCT measurements recommended; irrespective of PCT levels, clinical signs and symptoms remain the deciding factors in initiating or discontinuing antibiotics.

Successful implementation of PCT in a hospital requires not only in-depth training of staff (e.g., via in-house training provided by colleagues experienced in the use of PCT) but also that decision structures (including previously established ABS programs) are adapted to the PCT algorithms. Where this succeeds, PCT directed treatment can help reduce antibiotic associated complications, mortality, and antibiotic use.

Interleukin-6 (IL-6)

IL-6 belongs to the group of **pro-inflammatory cytokines** which are released by immune cells (e.g., macrophages) but also from endothelial and mesenchymal cells right at the beginning of an inflammatory reaction. Together with other cytokines, IL-6 induces the acute phase reaction and therefore also leads to the production of CRP. Production of IL-6 is triggered by viruses, bacterial components such as lipopolysaccharide (LPS), tissue trauma, and cellular hypoxia, with bacterial sepsis typically resulting in high serum concentrations of IL-6 [38].

IL-6 is currently viewed as the fastest routinely available biomarker, enabling the earliest possible detection of inflammatory processes. As such, IL-6 is superior with regard to sensitivity and specificity at an early point in time when compared with other markers.

IL-6 levels increase in response to an inflammatory stimulus up to 24 hours prior to the appearance of clinical signs and symptoms such as fever [39]. When compared to IL-6, CRP levels increase and reach a maximum at a significantly later point in time (Figure 2). As such, raised IL-6 levels at admission to intensive care were shown to be a good predictor of later evidence of bacteraemia [40]. Furthermore, raised IL-6 levels can be detected from a very early point on in patients with postoperative infections [41]. Whilst increased postoperative IL-6 concentrations fall rapidly in those without infection, significantly raised levels together with a delayed decrease

in the following days are associated with infectious complications [41]. It follows that the plasma IL-6 level has a possible bearing as an **early marker** especially for incipient complications in intensive care patients.

As IL-6 levels correlate well with **disease severity,** they can, in addition to diagnosing infections at an early stage, be used to identify high-risk patients and to adapt their treatment accordingly. IL-6 concentrations above 1000 pg/ml at the point in time the patient developed fever, for example, indicated incipient complications in intensive care patients earlier than other parameters could [38]. A recently published meta-analysis was also able to show a certain utility of plasma IL-6 concentrations for e.g., diagnosing bacterial sepsis in critically ill patients [42].

IL-6 also seems suited as a **marker of patient prognosis** [43, 44]. Amongst other conditions this has been confirmed for patients with sepsis, septic shock, those with fever, and patients with peritonitis [43]. For septic patients IL-6 levels correlated not only with lethality but also with the degree of sepsis, the extent of organ dysfunction and the occurrence of septic shock [44]. A prospective study involving 253 septic patients showed that increased IL-6 levels correlated with the risk of mortality. In contrast, high CRP levels showed no such association [45]. A prospective cohort study looking into the mortality of community acquired pneumonia one year post discharge from hospital demonstrated that increased IL-6 levels at the time of discharge were associated with a greater risk of mortality. High IL-6 levels were associated with death from cardiovascular disease, malignant tumours, infections, and renal failure in particular [46]. In addition, in surgical patients, IL-6 levels can indicate the severity and extent of tissue trauma [47]. Even though numerous studies have demonstrated the prognostic value of IL-6 especially in the early phase, the further course and patient prognosis seem better estimated with repeat PCT measurements than IL-6 monitoring [48].

A limitation of IL-6 which should be noted is that increased levels can have **non-infectious origins**, examples of which include

- postoperative complications such as acute wound failure following major abdominal surgery,
- severe trauma,
- burns,
- transfusion reactions,
- pyrexia of unknown origin in neutropenic patients [43].

Despite these limitations the early increase in IL-6 levels can potentially make for more rapid diagnosis, risk stratification and initiation of treatment when compared to CRP and PCT levels.

The rapid increase in IL-6 levels especially in the early phase of an infection adds to the diagnostic value of this parameter. Increased IL-6 levels may even be detectable before clinical signs and symptoms become apparent, which in turn may make for a more rapid determination of the risk of infection or sepsis, permitting earlier risk stratification. As such, the IL-6 level can usefully complement the pre-existing routine panel of infection biomarkers.

Conclusion

The safe diagnosis of an infection still commonly relies on **direct isolation of a pathogen on culture**, a process inherently associated with a relevant delay. A noteworthy characteristic of most clinical studies is the ambiguity and inconsistency with which clinical and microbiological features are defined. Early diagnosis of infections, and especially so in the case of sepsis, is generally unspecific because there are currently no valid methods available for directly detecting the underlying infection or predicting the transition from a limited localised infection to sepsis. As such, the initial diagnosis of a (suspected) infection is still based on **clinical signs and symptoms** and the **classic markers of inflammation**, which exhibit low specificity. Sepsis is not diagnosed until both infection is suspected and infection-associated organ dysfunction has become manifest. Specific detection of infections before they go on to cause sepsis and sepsis-associated organ dysfunction would be highly desirable; as such, **markers of inflammation** play an ever-increasing role in diagnosing and assessing infections, and monitoring their course. The biomarkers of inflammation discussed in this article can complement or aid clinical decision making; they can point to a bacterial origin of systemic inflammation and help stratify severity. In the end, however, clinical signs and symptoms remain the decisive factors whilst the biomarkers presented here can be useful in monitoring the course of an infection and objectifying treatment decisions such as discontinuation of antibiotics.

Markers of infection can increase diagnostic precision (especially in those cases where signs and symptoms are inconclusive). They are no substitute for an understanding of both intensive care medicine and infectiology, which remains a decisive factor in the light of which markers of infection should be interpreted. A selective approach to the use of markers of infection, taking their respective strengths and weaknesses into account, would seem to be advantageous. The biomarkers presented here should be seen as helpful tools which can aid – especially in the setting of intensive care medicine – in optimising decision making in the context of antibiotic treatment.

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