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Using procalcitonin (PCT) to improve the odds in sepsis management

SEPSIS • DETECTION

Disclaimer

This guide provides information for healthcare professionals on the optimal use of procalcitonin (PCT) testing and the subsequent interpretation of the results. However, the information contained in this guide does not relieve the healthcare professional of the obligation to verify the interpretation of PCT and other laboratory results based on clinical knowledge and assessment of the clinical status of each individual patient.

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Introduction

Sepsis is a serious medical condition that presents a considerable **diagnostic challenge** to emergency departments and intensive care clinicians. Sepsis is today considered as a dysregulated systemic reaction to a severe infection [1]. The condition can worsen within hours, rapidly becoming life-threatening. Over the past decade, many hospitals have adopted recommendations from the Surviving Sepsis Campaign (SSC)* for the management of septic patients, resulting in significantly improved survival rates [2]. Nevertheless, sepsis mortality rates are still unacceptably high, at around 15-25 % for patients with sepsis, reaching levels of 30-50 % in septic shock [3].

There are more cases of sepsis than of lung-, breast-, prostate-cancer and HIV combined (Fig. 1). **The incidence of sepsis has increased over time**, although this may be related to better reporting [4]. With sepsis being more prevalent in the elderly and in patients with comorbidities it is likely to become an even greater challenge in the future as both populations are increasing. As the pathogenesis of sepsis is not fully understood and no specific sepsis treatment is available, **early sepsis recognition is vital** so that curative and supportive measures can be implemented without delay. **Optimal clinical management has a clear impact on outcome.**

Sepsis is one of the most common diseases

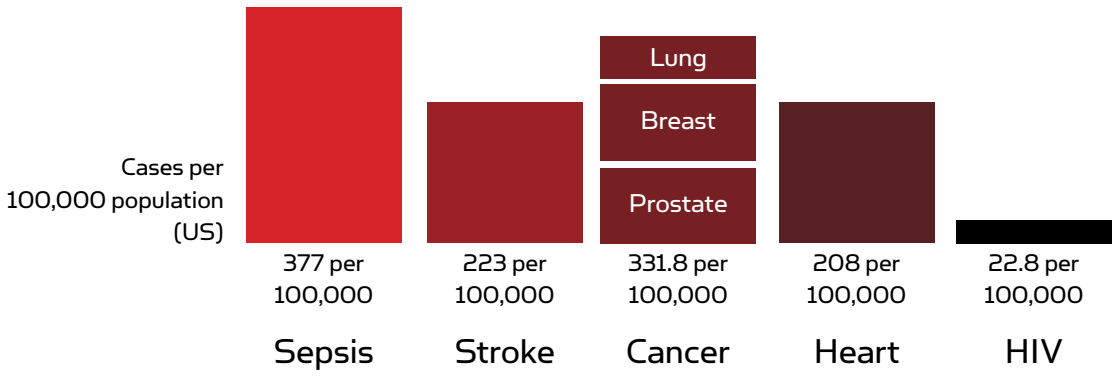

FIG 1: Illustration adapted from www.world-sepsis-day.org

*The European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) spearheaded the Surviving Sepsis Campaign more than two decades ago, and published the initial SSC guidelines in 2004 with the intention of providing guidance for the clinician caring for patients with sepsis or septic shock. Since the first publication, the guidelines have been updated in 2008, 2012 and most recently, in 2016. The ESICM remains committed to the continual improvement of these guidelines.

Definition of sepsis and septic shock

Sepsis involves an elaborate host response characterized by the release of a vast array of mediators with multiple effects on the cells, resulting in a complex metabolic response [5]. This host reaction is triggered by the release of various cytokines, which are small molecules that influence neighboring cells. The severity of the sepsis is directly related to the severity of all its components, including the inflammatory reaction.

It has sometimes been suggested that there may be a progression from sepsis to septic shock.

Today these states are presented as a pyramid of severity (Fig. 2). Sepsis is recognized by organ dysfunction caused by a dysregulated host response to infection, and septic shock by the additional presence of altered tissue perfusion, associated with elevated blood lactate levels and typically requiring vasopressor support [1,6].

The cause of sepsis

In the majority of cases, sepsis is caused by bacterial infections, but viruses, fungi and parasites can also be responsible.

The pyramid of infection severity

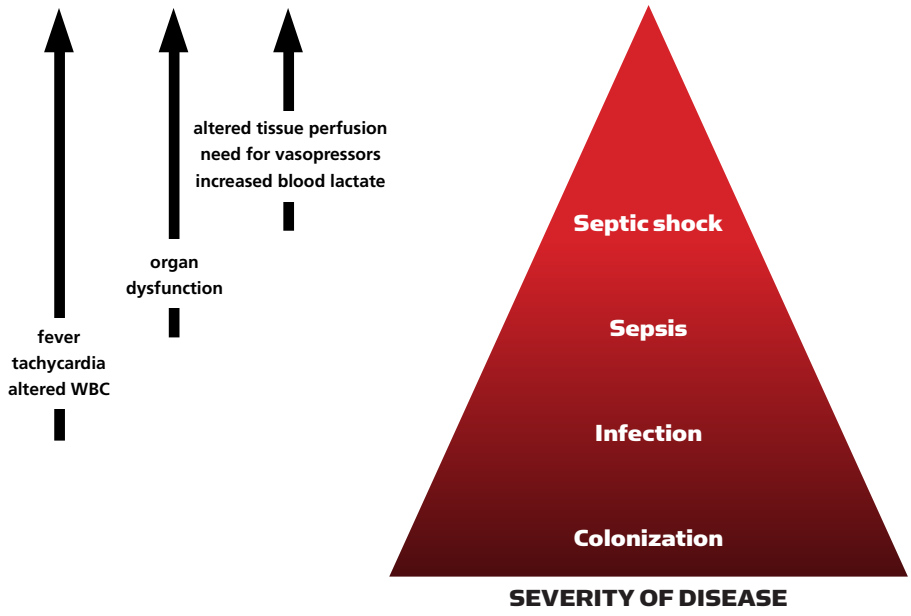

FIG. 2: Adapted from Vincent JL *et al.* Sepsis: older and newer concepts. Lancet Respir Med 2016;4: 237-40

Screening for sepsis and performance improvement

Patients with sepsis frequently present in the emergency department (ED) with various diagnoses, including different sources of infection [7]. SSC guidelines recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients [2].

Performance improvement efforts for sepsis are associated with improved patient outcomes. Successful programs should include protocol development and implementation, targeted metrics to be evaluated, data collection, and ongoing feedback to facilitate continuous performance improvement [2].

The importance of early detection of infection and sepsis is further highlighted by the mortality rates in cases of septic shock which can be as high as 50 %. Several publications have reported the effect of late detection and delayed treatment of infection. Any such delay in starting effective antibiotic therapy results in increasing mortality rates in sepsis and septic shock. An early publication reports an **increasing mortality rate in septic shock of 7.6 % with every hour of delayed start of antibiotic therapy** (Fig. 3) [8]. Although more recent papers report lower numbers [26-28], it is clear that early detection of sepsis, and undelayed start of appropriate antibiotic therapy save lives.

Early treatment of infection in patients with septic shock improves survival

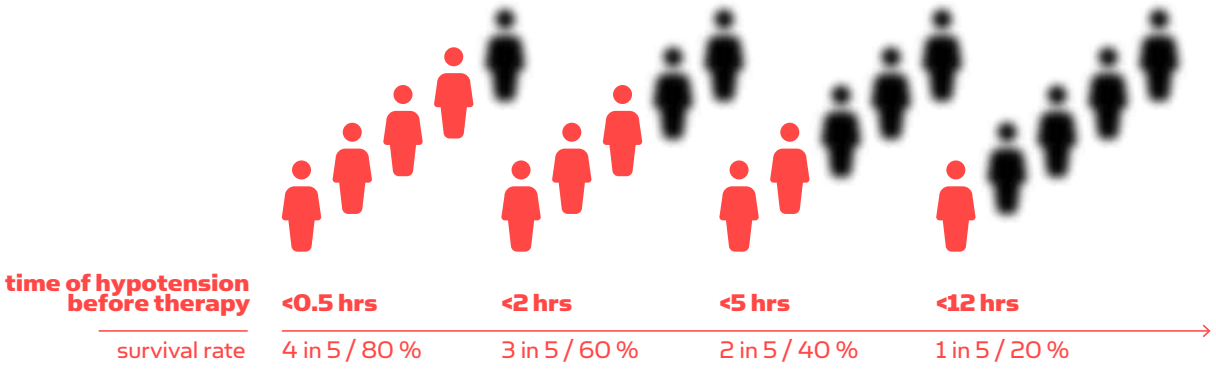

FIG. 3: Data derived from Kumar A, Roberts D, Wood KE *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34: 1589-96

Management of sepsis

Sepsis management involves two major components: treatment of infection and hemodynamic stabilization with intravenous fluids and the addition of vasoactive agents when required (Fig. 4).

Treatment of sepsis requires early, effective antibiotic administration [8, 26-28] as well as early source control when indicated. Without early effective treatment, the risk of major complications increases rapidly.

A combination of meaningful diagnostic tools and effective therapeutic measures is key to enhancing the medical management of patients with sepsis [2].

Among the diagnostic tools available today are biomarkers and specifically procalcitonin is widely acknowledged as the most sensitive biomarker to aid in the diagnosis of bacterial infection and sepsis [16, 20].

Essential aspects of sepsis management

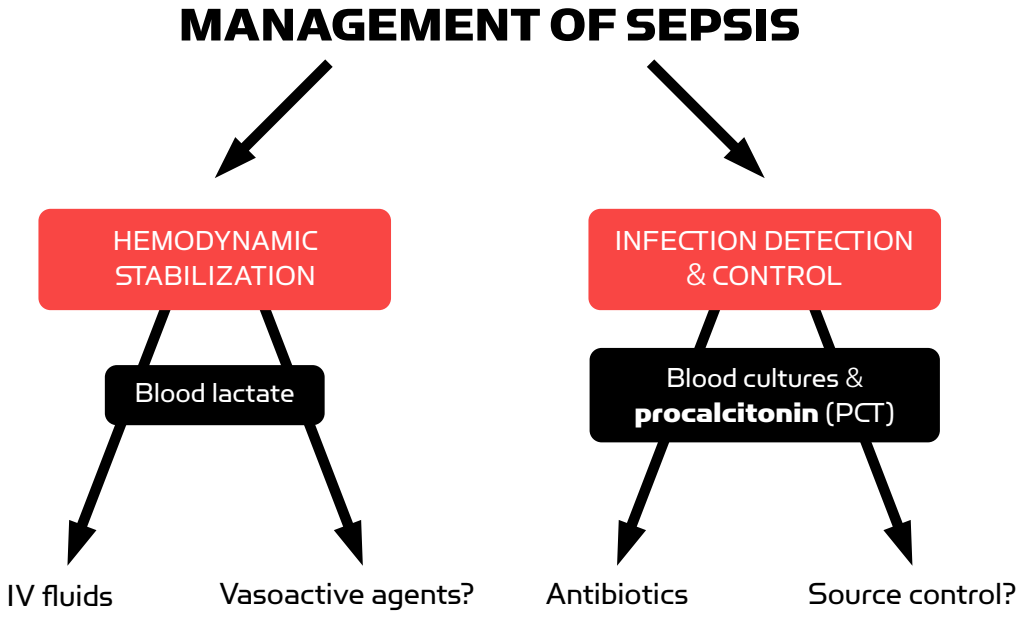

FIG. 4: Adapted from Vincent JL, personal communication

Procalcitonin (PCT)

PCT is a 116 amino acid prohormone of calcitonin that is expressed primarily in C cells of the thyroid gland and to a lesser extent in the neuroendocrine tissue of other organs, e.g. lungs and intestines.

PCT is a stable protein in plasma and blood samples. At room temperature, more than 80 % of the initial concentration can be recovered after 24 hours of storage, and >90 % when the sample is kept at 4 °C.

Several inflammatory cytokines and especially bacterial endotoxins can stimulate systemic production of PCT in various tissue types [9]. Consequently, cytokines and/or bacterial endotoxins, especially during systemic bacterial infections, trigger increased plasma levels of PCT. PCT observed during systemic bacterial infections are typically higher than levels in most non-infectious inflammatory states and in patients with infections of viral or fungal etiology [10].

Compared to **C-reactive protein (CRP)** - a biomarker often used to aid in the diagnosis of inflammation and infection - PCT levels show an earlier increase in the event of bacterial infection, as well as faster decreasing levels when the infection has lessened [11] (Fig.5).

These favorable kinetics potentially enable earlier diagnosis of sepsis and better monitoring of its progression. The **primary utility of PCT** is therefore to help uncover the presence of systemic bacterial infections and sepsis, and numerous studies have investigated the potential roles of PCT in diagnosis and management of local and systemic infections [12, 13, 14].

PCT not only complements CRP, but also complements **lactate** in the risk stratification of patients suspected of having infection [15]. As a measurement of hemodynamic stabilization and tissue hypoperfusion, lactate is essential in the management of sepsis and septic shock.

Kinetics of several biomarkers after a bacterial challenge

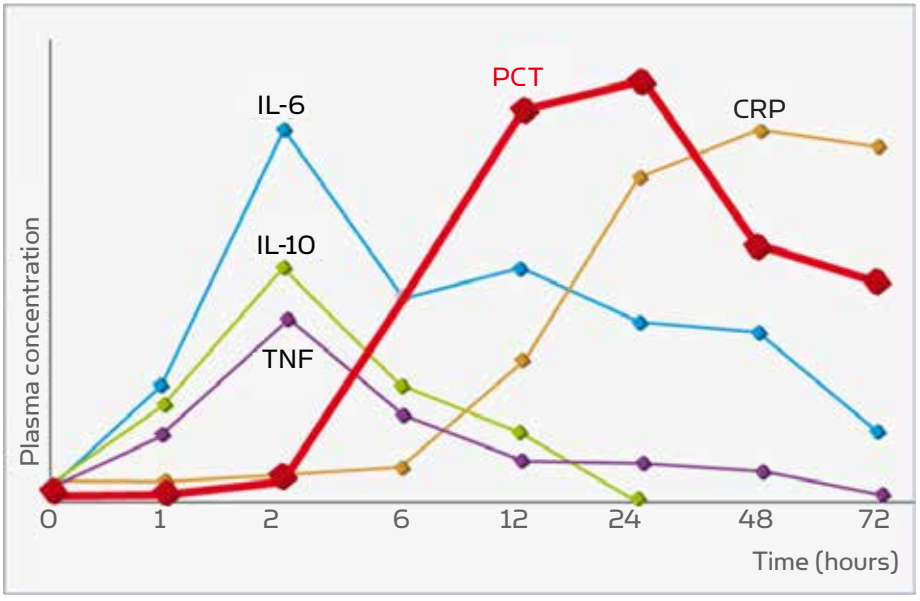

Fig. 5: Adapted from Meisner; Procalcitonin: Experience with a New Diagnostic Tool for Bacterial Infection and Systemic Inflammation. J Lab Med 1999, 23 (5); 263-272

PCT testing for early diagnosis and rule-out of sepsis

PCT has a high sensitivity for most types of bacterial infection and a negative predictive value of >95 % [13, 16].

This means that negative PCT results (<0.25 ng/mL in the ED, and <0.5 ng/mL in the ICU) strongly support the rule-out of sepsis [16, 19, 22]. Such findings can help physicians optimize the management of these patients, e.g. suggesting that antibiotic therapy could be withheld and/or other disease states should be looked for.

Repeat test to confirm result

If there is a strong suspicion of bacterial or fungal infection, but an initial negative PCT result, the test should be repeated. If a second test, conducted 6-24 hours later, confirms the initial negative result, there is very low risk of an ongoing systemic non-viral infection (Fig. 6, Table I).

Procalcitonin values correlate with increasing severity of infection and sepsis

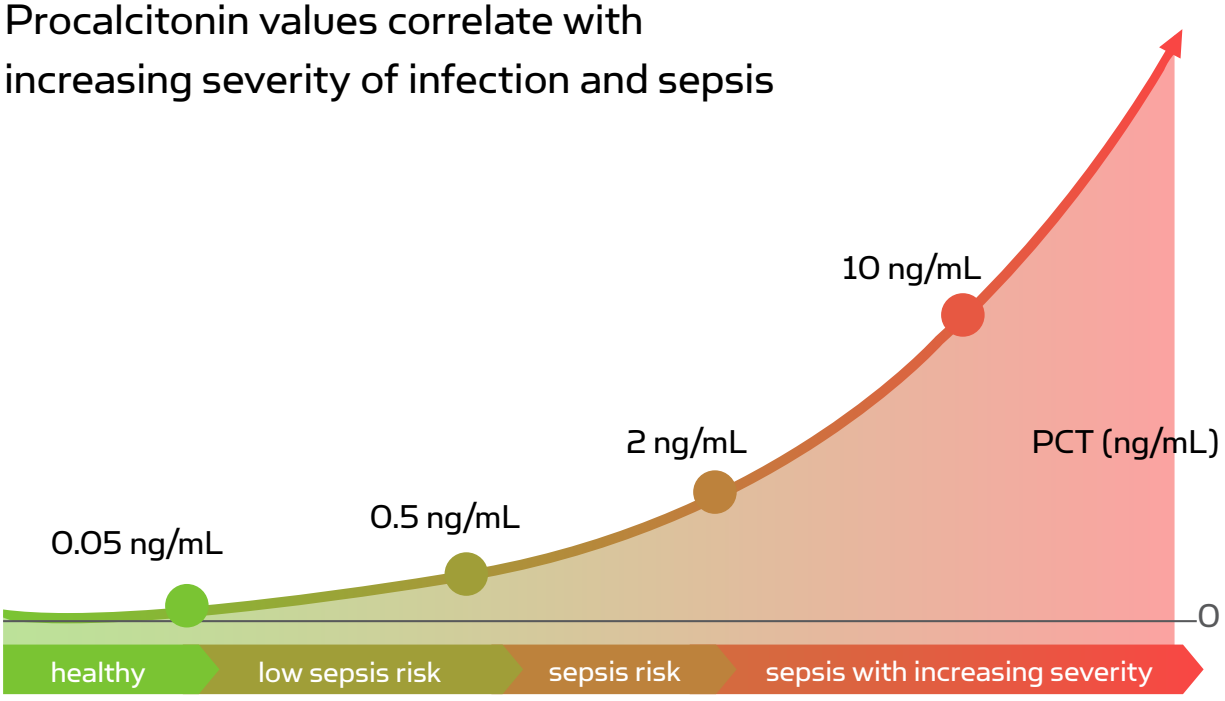

FIG. 6: Procalcitonin values in patients with increasing severity of infection and/or sepsis in an ICU setting.

Adapted from McGee *et al.* Procalcitonin, clinical utility in diagnosing sepsis. Clin Lab News 2009 July: 35(7): 1-8

Diagnosing sepsis: The added value of PCT

Before starting any antibiotics, samples must be taken for blood culture and any other methodology to identify the presence of bacteria and sometimes other suspected microorganisms (fungi, viruses, parasites) [2].

Microbiological tests of specimens such as sputum, urine or pus only provide useful information in a minority of cases. Collection of blood cultures is of great value to identify causative microorganisms and to study resistance patterns. Regrettably, blood cultures offer modest sensitivity and specificity, and often generate false negatives and false positives results. In addition, blood culture results are, in most cases, not available until at least 24 hours after the blood collection [19]. **To complement blood cultures, biomarkers may be used to aid in early diagnosis.** This enables earlier and more effective management [19].

PCT has high accuracy for diagnosis of sepsis in various settings [20]. **The lag time for PCT induction is approximately 2-4 hours after the onset of sepsis,** a time period that has usually passed in patients presenting to the emergency department [20].

As there are several potential causes of elevated PCT levels, PCT testing offers a modest specificity for sepsis and, consequently, a modest positive predictive value. Other potential causes of elevated PCT levels include the first day(s) after a major trauma, severe burns, major surgery, birth (~age less than 48 hours) and treatment with drugs stimulating the release of inflammatory cytokines. Patients with prolonged or severe cardiogenic shock, organ perfusion abnormalities, small cell lung cancer or medullary C-cell carcinoma of the thyroid can also have elevated PCT levels [20].

PCT levels ≥0.5 ng/mL

PCT levels of ≥0.5 ng/mL mean that the levels of PCT are increased. Although sepsis is not certain and other causes of these increased PCT levels should be considered, the findings warrant repeat testing 6-24 hours later to validate the first result and, if infection cannot be excluded or is suspected, empiric antibiotic treatment should be initiated without delay (Table I, Fig. 7) [25].

PCT levels >2.0 ng/mL

Finding initial PCT levels of >2.0 ng/mL strongly suggests systemic infection with high risk of sepsis. Patients with sepsis usually have circulating PCT plasma levels of >2 ng/mL and these correlate well with severity of disease [17], with higher levels indicating a greater degree of severity (Fig. 6, Table I).

Empiric antibiotic therapy should be initiated immediately, and the patient referred to ICU. It is recommended to retest with PCT regularly to ensure that the patient is responding to the treatment. In case of treatment failure, indicated by consistently increased or increasing PCT values, alternative treatment should be considered (Table I, Fig. 7 and 8) [25].

PCT concentration in the blood: Reference ranges and interpretation

PCT <0.05 ng/mL	• Values found in healthy individuals (age ≥3 days) • No indication of inflammation or infection
PCT <0.5 ng/mL	• Measurable, but clinically insignificant inflammatory response • Local inflammation or infection possible • Low risk of sepsis
PCT ≥0.5 and <2.0 ng/mL	• Significant, but moderate systemic inflammatory response • Infection is possible, but other conditions are also known to cause such PCT levels (e.g. severe trauma, surgery, major burns, cardiogenic shock) • Sepsis likely in case of proven infection (fungal or bacterial) • **Follow-up of PCT levels recommended (6-24 hours)**
PCT ≥2.0 and <10 ng/mL	• Severe systemic inflammatory response, most likely due to systemic bacterial infection and sepsis, unless other causes are known (see above) • High risk of developing multi-organ dysfunction • Poor outcome • **Daily measurement of PCT levels recommended** • If values are persistently elevated, reconsider sepsis therapy
PCT ≥10 ng/mL	• Severe systemic inflammatory response, mostly linked to bacterial sepsis or septic shock • Frequently associated with severe multi-organ dysfunction • High risk of lethal outcome • **Daily measurement of PCT levels recommended** • If values are persistently elevated, reconsider sepsis therapy

TABLE I: PCT reference ranges and interpretation of plasma levels in an ICU setting.

Adapted from McGee *et al*. Procalcitonin, clinical utility in diagnosing sepsis. Clin Lab News 2009 July: 35(7): 1-8

NOTE: PCT test results should always be interpreted within a comprehensive clinical context

PCT-guided use of antibiotic therapy

De-escalation of antimicrobial therapy is a mainstay of antibiotic stewardship programs and is associated with **less resistant microorganisms, fewer side effects, and lower costs** (SSC guidelines 2016) [2].

SSC guidelines 2016 suggests that measurement of procalcitonin levels:

- can be used to **support shortening the duration** of antimicrobial therapy in sepsis patients
- can be used to **support the discontinuation** of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection

Antibiotic therapy (ABx) should be reassessed as soon as microbiological information is obtained. The antibiotic spectrum should be reduced (de-escalation) wherever possible. If there is no evidence of infection, ABx could even be stopped.

A number of clinical studies have proven the effectiveness and safety of PCT-guided therapy [12, 17, 21, 22, 23, 24]. Guided by PCT measurements, the duration of ABx in patients in both ED and ICU settings was shortened consistently by several days, without compromising clinical safety [17, 23, 24].

PCT algorithms in ED and ICU

A recent paper offers recommendations on antibiotic management based on PCT levels found in the ED in patients with suspected infection or sepsis (Fig. 7) and PCT levels found in the ICU in patients with suspected infection or sepsis (Fig. 8) [25].

Procalcitonin (PCT) algorithm in patients with respiratory tract infections in ED

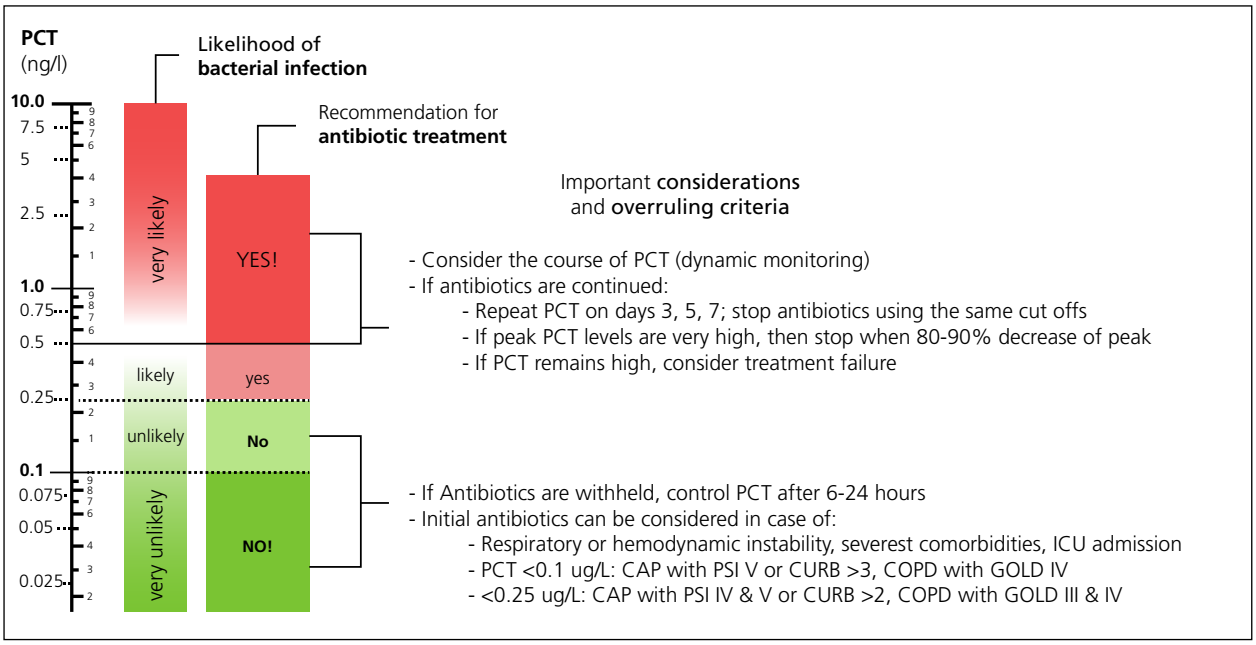

FIG. 7: Adapted from Sager *et al*. Procalcitonin-guided diagnosis PCT and antibiotic stewardship revisited. BMC Medicine 2017; 15:15.

Abbreviations: CAP: Community Acquired Pneumonia; PSI: Pneumonia Severity Index; CURB: Confusion, Urea, Respiratory rate, Blood pressure - Score; COPD; Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease

Procalcitonin (PCT) algorithm in patients with sepsis in ICU

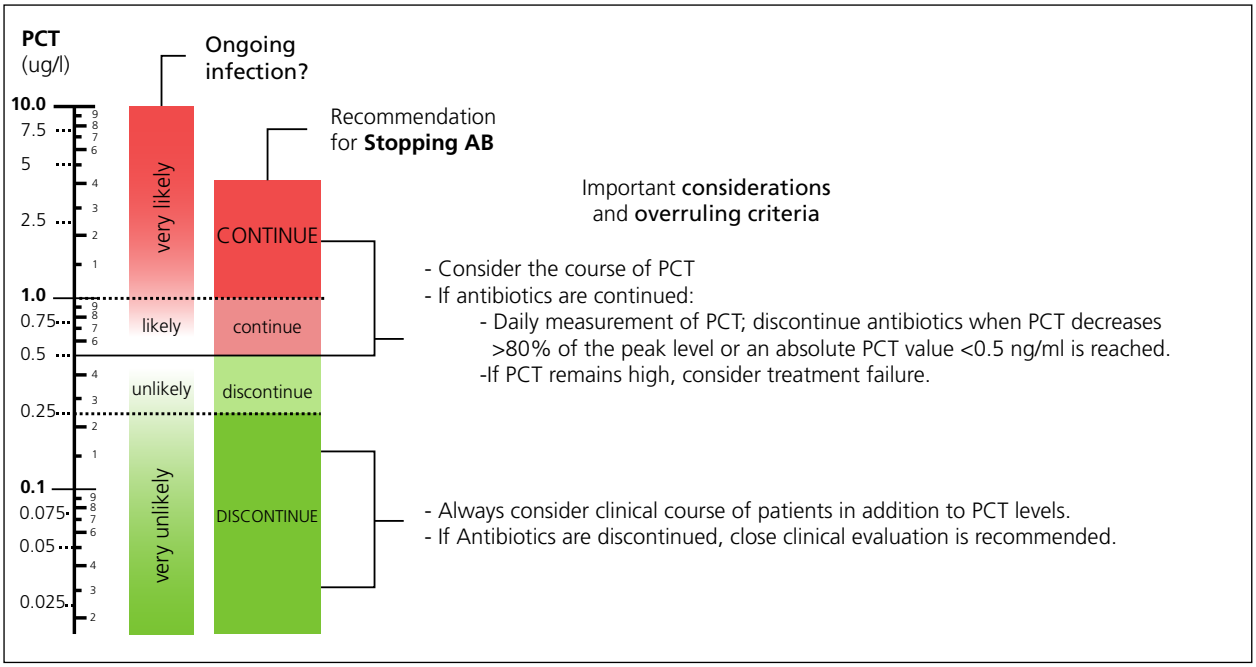

FIG. 8: Adapted from Sager *et al*. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Medicine 2017; 15:15.

Data from an ED setting

In a randomized intervention study [17], 302 consecutive patients admitted to ED with suspected community-acquired pneumonia (CAP) were included. Patients were assessed at baseline, after 4, 6, and 8 days, and after 6 weeks.

The control group (n=151) received ABx according to usual standard of care, while in the PCT group (n=151) ABx was recommended based on PCT concentrations detailed below and summarized in Fig. 8 [17, 23]:

Patients not on ABx during admission:

- Plasma PCT levels of ≤0.1 ng/mL indicated absence of bacterial infection; use of ABx was strongly discouraged
- PCT levels of >0.1 and <0.25 ng/mL indicated bacterial infection to be unlikely, and use of ABx was discouraged
- PCT levels of ≥0.25 and <0.5 ng/mL indicated possible bacterial infection, and start of ABx was recommended
- PCT levels of ≥0.5 ng/mL suggested presence of bacterial infection, and start of ABx was strongly recommended

For patients on ABx during admission:

- In case of PCT levels of <0.25 ng/mL, ABx should be discontinued.

In both control and PCT-guided group, re-evaluation 6-24 hours after admission was possible in patients, in whom antibiotics were withheld, including clinical and laboratory work-up and re-measurement of PCT values in the PCT-guided group. Procalcitonin levels were reassessed after 4, 6, and 8 days.

Antibiotics were discontinued on the basis of the procalcitonin cut-offs defined. In patients with very high PCT values on admission (e.g. >10 ng/mL), discontinuation of antibiotics was encouraged if levels decreased to less than 10 % of the initial value (e.g. <1 ng/mL instead of <0.25 ng/mL).

During the study, **PCT guidance reduced total antibiotic exposure, antibiotic prescriptions on admission, and antibiotic treatment duration in patients with negative blood culture results compared to the standard-of-care group.** In patients with positive blood cultures, no difference in ABx duration was observed (safety end-point). The outcome was similar in both groups, with an overall treatment success rate of 83 % [17].

With PCT guidance for the initiation and duration of ABx, most gain was observed during the first few days of treatment, when almost one third of the patients guided by PCT levels had ABx discontinued (Fig. 9).

PCT guidance reduces duration of antibiotic exposure

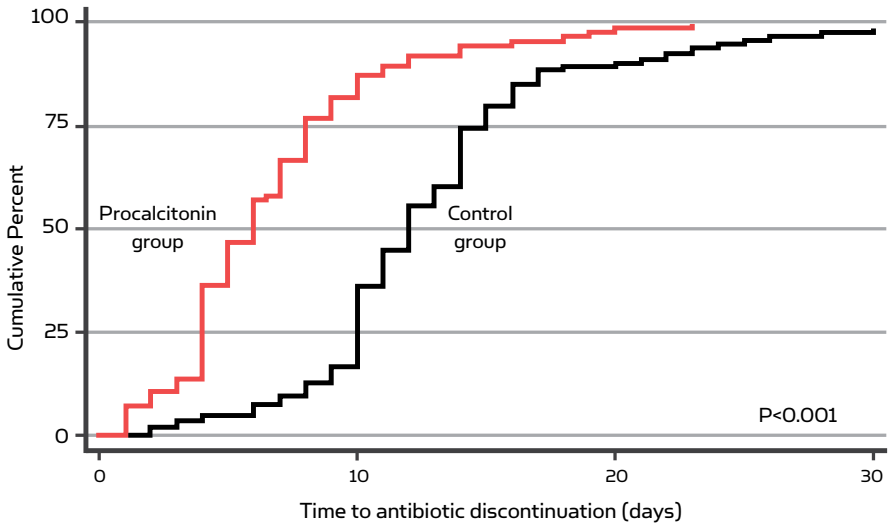

FIG. 9: Adapted from Christ-Crain M, Stolz D, Bingisser R *et al*. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006; 174: 84-93

Data from an ICU setting

Similar guidance for ABx in other settings, such as the ICU, has been proposed and tested in clinical studies. The effect of a PCT-based algorithm on antibiotic use in the ICU was tested recently by Bouadma *et al.* and demonstrated a significant reduction in the time patients are on antibiotics [24]. After a week in ICU, over 80 % of the control patients were still treated with antibiotics, while in the group of patients tested with PCT this number was reduced to 44 % (Fig. 10). In brief, patients tested for PCT levels were 2.7 days (19 %) less on antibiotic treatment than controls while mortality in both groups was the same.

Reduced treatment duration has also been shown in other studies [21, 22] applying various PCT levels to guide ABx in different ICU settings and patient groups. **Consistently, patients in the PCT-guided groups had shorter ABx courses than those in the control group with the same clinical outcome, demonstrating the safety of PCT-guided ABx.**

PCT reduces antibiotic use in the ICU

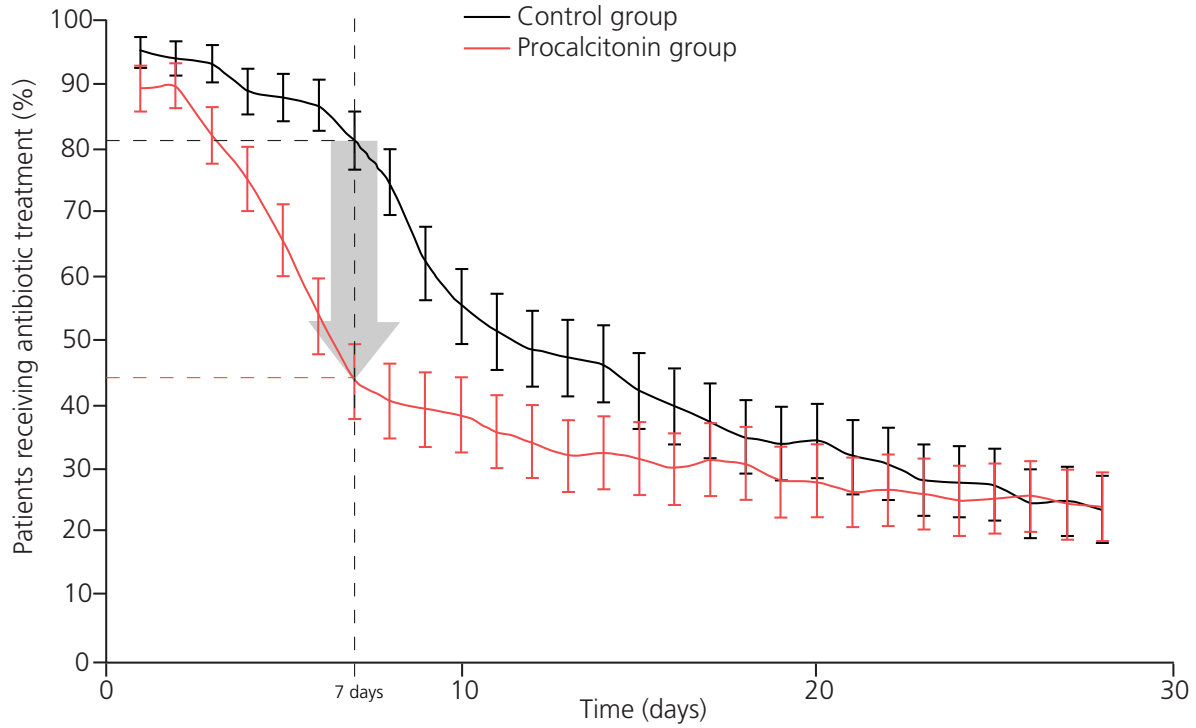

FIG. 10: Effect of PCT testing on antibiotic use in the ICU [24], adapted from Bouadma L, Luyt C-E, Tubach F *et al.* Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010; 375: 463-74

The value of point-of-care testing (POCT)

When a biomarker supports immediate therapy decisions, a fast and accurate POC result provides more than convenience, it will add value to clinical workflow and patient management [29]. **Typical observations associated with POC testing are the shorter turnaround time (TAT), shorter length of stay in ED, and shorter times between door and non-treatment.** Like other biomarkers such as troponin and D-dimer, there is also great benefit of measuring PCT levels at the point of care.

In current general practice, patients with symptoms suggestive of bacterial infection are treated with a broad-spectrum antibiotic, just in case. Often, however, such symptoms have a pulmonary (e.g. COPD) or even cardiovascular etiology (e.g. CHF, AHF). Unjustified use of antibiotics is very likely associated with the emergence of multi-resistant bacteria (MRSA, etc.) [30], and can even be harmful to patients, especially when the real clinical cause of the symptoms is related to heart failure [31].

PCT levels below defined cut-offs for likely bacterial infection (Fig. 7 and 8) support the treating clinician in withholding antibiotic therapy and consider other causes than infection in patients with symptoms suggesting this. Many elderly patients are admitted to ED with unclear symptoms suggestive of infection, often at times when limited STAT support from the clinical lab is available.

Values above the cut-offs, on the other hand, would support the undelayed start of antibiotics. Serial follow-up testing can reflect the success or failure of the chosen therapy.

PCT samples are collected throughout the patient's stay in the hospital and typically come from various departments (ED, ICU, clinical wards, etc.). When testing is performed on different diagnostic platforms in different locations, it is essential that these different assays have excellent diagnostic agreement and preferably apply the same cut-off points and present the same absolute results. Such concordance between assays also eliminates the need of any additional training of medical staff for correct interpretation of the results.

In general, POC testing provides faster and more conveniently important diagnostic information, essential for optimized patient management in the ED and the ICU [29].

PCT to fight sepsis

- Sepsis is a serious medical condition and represents a considerable diagnostic challenge to emergency department and intensive care clinicians [1, 2]
- Any delay in effective antibiotic therapy dramatically reduces survival rates [7]
- De-escalation of antimicrobial therapy is associated with less resistant microorganisms, fewer side effects, and lower costs [2, 22]

The value of PCT

- PCT testing aids early diagnosis and rule-out of sepsis [16, 19]
- PCT testing aids in the risk stratification of patients with suspected infection and sepsis [15]
- PCT-guided antibiotic management has been proven to shorten antibiotic therapy without compromising patient safety [17, 21, 22, 23, 24, 25]

PCT improves the odds in sepsis management

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