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Hot Topic

Hot topics on procalcitonin use in clinical practice, can it help antibiotic stewardship?

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1. Introduction

In the past 15 years, considerable research has been conducted on procalcitonin (PCT) in the fields of sepsis, respiratory tract infection and antibiotic stewardship. An international group of experts recently produced a consensus document addressing optimal use of PCT in clinical practice, including prerequisites for implementation into clinical protocols and work flow [1]. However, despite advances and several studies investigating the role of PCT in medical/surgical care, there are still many controversial areas with regards to diagnostic utilities of PCT in certain conditions and its impact on antibiotic stewardship. In this review, several 'hot topics' on PCT were selected and reviewed by members of the "Rapid Diagnostic and Biomarkers" of the International Society of Antimicrobial Chemotherapy (ISAC). This group, established in the second half of 2018, includes scientists, microbiology and infectious diseases clinicians and academics, whose aim is to advance the education and science of infection management. This paper is an in-depth review of the current literature that addresses areas where there are limited studies, evidence and clinical experience on the utility of PCT. The review summarises the various aspects of PCT utility and provides expert opinions and insights from the authors' own experience, highlighting areas for future study and research.

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2. Use of "time zero" PCT in initiation and tailoring of antibiotic therapy

Early recognition of sepsis is key for better outcomes. Delays in appropriate antimicrobial therapy might hinder survival; however, there has been recent debate on the impact of the timing of antibiotic administration. Emergency departments (EDs) are at the frontline of recognition and early treatment of septic patients. In the ED there are three key questions when faced with a patient with suspected infection: Should antibiotics be initiated? If yes, which ones? Does the patient need to be admitted? The answers to these questions are not simple because clinical scores alone to detect sepsis in the ED are neither specific nor sensitive enough to support early diagnosis [2]. This is mainly due to the complicated pathophysiology of the septic process and the individual patient response to infection, because the immune response starts from the time of infection insult ("time zero") and the trajectory for PCT and other markers as well as the physiological response may vary depending on the time of presentation to the ED.

Furthermore, clinical scoring systems, e.g., sequential organ failure score (SOFA), mortality in emergency department sepsis (MEDS) score, and, lately, the national early warning scores (NEWS) [3,4], used alone are neither sensitive nor specific in identifying infection or predicting deterioration. The concept of PIRO (Predisposition, presence of Infection, immune Response and Organ dysfunction) may help identify septic patients as early as possible [5]. However, a better way is to combine both novel biomarkers and clinical scoring systems [2] at the earliest opportunity during a clinical consultation to identify infection and those patients at risk of deterioration.

A study of 295 patients that targeted the use of PCT as a marker of bacteraemia in the ED showed a sensitivity of 75%, a specificity of 79.8% and a positive predictive value (PPV) of 16.9%, but a very convincing negative predictive value (NPV) of 98.2%, area under the receiver-operating characteristic curve (AUROCC) measurement of 0.79 and an accuracy of 89.8% for PCT [6]. The PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) study involving 714 patients focused on PCT tailored vs. conventional antibiotic treatment. The PCT group had significantly more days (mean difference 2.7 days) without antibiotics, with a relative reduction of antibiotic exposure of 23%. However, there were some limitations of this study: 10% of the patients had surgical problems and protocol adherence was not satisfactory (the protocol was not followed in 219 cases) [7].

Early PCT measurement in the ED is indicated in patients with dyspnoea. PCT has an established role in antibiotic guidance in respiratory infections, a common indication for antibiotics in patients with dyspnoea. However, the use of PCT in cardiac patients is less straightforward because some cardiac patients without bacterial infection may have raised PCT. Patients with heart failure have a degree of tissue hypoperfusion; if this is severe enough to cause gut wall ischemia, this can lead to increased bowel permeability, bacterial translocation and endotoxin release [8]. A study focusing on patients with dyspnoea measured cardiac biomarkers, i.e., MR-proANP, BNP and NT-proBNP, along with PCT. Patients with elevated cardiac markers and PCT below 0.2 ng/mL were treated with diuretics. Patients with PCT above 0.2 ng/mL were started on antibiotic therapy with promising outcomes [9].

Despite high sensitivity and specificity for bacterial infection, single PCT measurements can be misleading. High PCT levels encourage the use of antibiotics in the ED; however, low readings ($\leq$0.2 ng/mL) might raise more questions and decrease compliance with protocols. Nevertheless, the initial management in the ED can be reassessed and decisions can be changed, if it is clinically safe to do so [1]. No single biomarker should be used in decision making; however, PCT and other novel biomarkers can be safely incorporated into clinical scoring systems to assist clinicians in deciding whether to administer antibiotics and to admit the patient.

3. Value of PCT in bacteraemia patients

Several studies have investigated the effects of PCT-guided antibiotic therapy in patients with systemic infection and sepsis [10,11]. A PCT-guided approach, particularly for respiratory infections, has resulted in shorter durations of antibiotic treatment with positive clinical outcomes, such as lower rates of antibiotic-related adverse events and mortality [10]. Nevertheless, there remains a concern about the effectiveness and safety of this approach in patients with bacteraemia, when physicians may be reluctant to reduce treatment duration regardless of PCT levels. Moreover, several guidelines recommend standard durations of therapy for most patients with true bacteraemia to protect against potential complications, such as endocarditis.

There are usually only small numbers of bacteraemia patients in individual studies, which makes it challenging to contend the safety of PCT-guided antibiotic duration in bacteraemic cases. However, a recent meta-analysis of individual data from 523 patients with bacteraemia (including *Staphylococcus aureus* bacteraemia) pooled from 13 clinical trials showed that PCT-guided antibiotic management in this population resulted in lower antibiotic exposure without apparent increase in mortality [12]. There were no comments on increasing risk of endocarditis in PCT-guided groups vs. classical treatment groups.

Clearly, PCT does not help identify pathogens or risk of antibiotic resistance; therefore, blood culture results are an important part of infection management and choice of antimicrobial therapy. Although blood cultures remain a cornerstone in identifying bacteraemic patients and should always be considered according to clinical needs and local guides, their probability of being positive increases with rising PCT levels. Using PCT to select patients for further microbiological and phenotypic investigations to detect systemic infections is a promising approach to improve the cost-effective and safe management of patients with infection and possible bacteraemia [13–15].

4. Procalcitonin in critically ill patients

4.1. Procalcitonin for initiating antibiotics in critically ill patients

Several observational studies have shown that time to adequate antibiotic treatment is a strong predictor of mortality in critically ill septic patients [16]. Furthermore, in the intensive care unit (ICU), physicians have few and rather imprecise measures to inform about the status of the patient (improving or deteriorating). Current markers like C-reactive protein (CRP) and white blood cells (WBC) are not sufficient to assist timely decisions about therapeutic changes. In addition, there is often a considerable delay in identifying the specific microbiological cause of sepsis, which is not helped by the rather low sensitivity of blood cultures, particularly in patients already receiving antibiotics. Novel methods to improve the timing of initial antibiotics and of changes in antibiotics are urgently needed.

Without source control, PCT continues to increase. Observational studies cannot fully determine whether PCT-guided antibiotic initiation and escalation can improve outcomes in critically ill septic patients. This issue was investigated in the Procalcitonin And Survival Study (PASS), a 1200-patient randomized, controlled multicentre trial, in which increasing PCT levels in the intervention arm patients led to empirical broadening of antibiotics according to a specified algorithm and prompted additional culture samples and radiological imaging of suspected infected foci [17]. Although the adherence to this antibiotic algorithm was relatively

high (82%), and the use of broad-spectrum antibiotics was in keeping with increasing PCT, and was higher overall than in the control group, the investigators failed to demonstrate a survival benefit of this strategy. There are several potential reasons for this outcome: i) "a neutralizing effect", whereby harm from antibiotics and benefit from better timing may have caused an overall negative result; ii) there was already sufficient antibiotic coverage in patients at high risk of mortality: the investigators demonstrated that the PCT-algorithm did not change the use of study drugs in the patients who were clinically judged to be most ill, but did in those clinically rated to have milder illness; iii) generally, it is very hard to change the prognosis of critically ill septic patients: many trials have failed to do this, possibly because mortality in such patients is also attributable to non-modifiable variables like age and co-morbidities. Thus, increasing PCT, in a broad, critically ill sepsis population should not be the only factor driving antimicrobial escalation.

4.2. PCT for antibiotic reduction

Based on the increasing use of broad-spectrum antibiotics and the associated increasing incidence of antibiotic resistance, the World Health Organization (WHO) has stated that: *"Antibiotic resistance is one of the biggest threats to global health, food security, and development today"* and *"Antibiotic resistance occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process."* Global awareness to revert this alarming development, including among critically ill patients, is high.

PCT-guided antibiotic discontinuation strategies have been proposed to assist in this task in sepsis and pneumonia and several studies have been conducted. All these studies include algorithms specifying when to stop antibiotics based on serial PCT measurements, typically with a combined fixed cut-off (e.g. encouragement to stop antibiotics when PCT <0.5 ng/mL) and a relative cut-off (e.g. to stop antibiotics when PCT was reduced by 80% from the peak level). The largest of these studies were the PRORATA trial [7] and the Stop Antibiotics on Procalcitonin guidance Study (SAPS) [18].

In the PRORATA trial, there was a significant reduction in the total number of days that the patient received antibiotics (2.7 days; $P < 0.001$), with no significant changes in mortality or other safety endpoints. However, there was a slight trend in 60-day mortality in favour of the control group. In the SAPS, duration of antibiotic treatment was also reduced by 2.7 days ($P < 0.0001$), and there was a reduction in mortality of 5.4% (P=0.0122) in the PCT-guided group.

Therefore, a strategy with daily PCT measurements and subsequent discontinuation of antibiotics when PCT is <0.5 ng/mL or reduced by 80% from the peak level can be expected to reduce the duration of antibiotic treatment by approximately 3 days. This strategy appears to be safe and may even reduce mortality. PCT-guided antibiotic initiation should only be within a clinical context and a raised PCT must not be a sole factor in initiating antibiotics [1].

4.3. PCT in critically ill patients with renal failure

Metabolism of PCT is not significantly influenced by kidney function because renal elimination is not the major metabolic pathway of PCT clearance. In patients with significantly impaired renal PCT excretion, plasma PCT levels do not increase simultaneously [19]; however, a cut-off of 0.8 ng/mL may be considered as the upper normal reference value in non-acutely infected haemodialysis patients [20]. Studies in patients with acute and chronic renal failure show that PCT is a useful marker of bacterial infections. PCT was massively elevated in the presence and absence of acute renal failure in sepsis patients [21]. Other studies indicate that both PCT and CRP tests have poor sensitivity but acceptable specificity in diagnosing bacterial infection in patients with renal impairment. Given the poor negative likelihood ratio, the role of PCT as a rule-out test is questionable [22]. A recent study concluded that high-volume continuous renal replacement therapy (HV-CRRT) can more effectively remove various inflammatory factors and reduce serum PCT for the treatment of pancreatitis complicated by acute renal failure. Replacing the blood filter at appropriate time-points can also improve treatment efficacy [23]. Serial PCT measurements should be considered in patients with renal failure, and renal replacement therapy and PCT values should be interpreted within a clinical context and should not be the sole factor in escalating or de-escalating antibiotics in these patients (see section 4).

5. Procalcitonin and nosocomial infections in the Intensive Care Unit: value of serial determinations

Sequential measurement of PCT in critically ill patients may enable early diagnosis of infection and potential benefits of early treatment (Table 1), [24–30] and is of interest from the prognostic point of view. High baseline concentrations of PCT are not always associated with a poor prognosis, and the prognostic ability of the initial concentrations in sepsis is controversial; the prognostic value based on the evolution of PCT levels may be more useful. The concept of PCT clearance that reflects PCT dynamics has been proposed to assess the behaviour of PCT and its relationship with prognosis [31].

6. PCT in burn patients

Tissue burns induce systemic inflammation, the extent of which is proportional to the extent and severity of burn injury [32]. It is beneficial to detect infections as early as possible in burn patients because the overchallenged immune system, secondary to the acute inflammation, might not respond as rapidly and effectively to infective agents as it would in otherwise healthy subjects.

In a 20-bed burn ICU involving 121 patients, PCT with a cut-off value of 0.69 ng/mL for sepsis prediction was associated with sensitivity of 89%, specificity of 85%, PPV of 82% and NPV of 88% Therefore, PCT proved to be an early indicator of septic complications and a tool for monitoring response to antimicrobial therapy [33]. In a retrospective observational study including 150 burn patients, biomarkers of sepsis were analysed: a panel of PCT, WBC and platelets, D-dimer, CRP, lactate and temperature measurements were compared in septic (n=102) and non-septic (n=48) patients. Although statistically significant differences between the two groups were detected for all the examined biomarkers, PCT at a cut-off value of 0.5 ng/mL proved to be the most accurate marker for predicting bacterial infection with the largest area under the curve (AUC) and effect size (AUC=0.71) [34].

The absolute amount of PCT is directly proportional to the severity of bacterial infections and sepsis in most patients, with survival potentially predicted by the dynamics and absolute amount of PCT [35]. In 101 burn patients, PCT was used for risk stratification in such terms. There were statistically significant differences between PCT levels of survivors (n=68) and non-survivors (n=33), but PCT also predicted the inadequacy of antibiotic therapy in a time course of 15 days, resulting in sepsis-associated death in patients with increasing amount of PCT despite antibiotic therapy [36]. Data related to PCT in burns patient are limited and more studies are needed to establish the impact of PCT and other markers on early diagnosis of infection and escalation of therapy.

Table 1
Some studies on sequential measurement of PCT in critically ill patients with certain healthcare-associated infections.

Category of infection	Studies	Ref
Trauma patients admitted in the intensive care unit (ICU)	Daily measurement of procalcitonin (PCT). Trauma patients with a septic complication demonstrated an early and significant increase in PCT compared with concentrations measured one day before sepsis diagnosis [0.85 (0.48–3.2) ng/mL vs. 3.32 (1–5.85) ng/mL, $P < 0.001$]	[24]
Critically ill patients with new onset of fever	PCT helped to predict ICU-acquired high-risk microbial infections (i.e., bloodstream infection [BSI] or septic shock) when peaked above 0.65 ng/mL and low risk infection when peaked below 0.65 ng/mL	[25]
Blood stream infection (BSI)	Charles et al. assessed the accuracy of PCT in the diagnosis of BSI in patients with primary and secondary sepsis. They showed that PCT elevation at the onset of sepsis is lower in patients with secondary sepsis-related BSI than in those experiencing their first episode of systemic infection, regardless of the severity of the disease. Diagnostic accuracy of PCT as assessed by the area under the receiver-operating characteristic curves (AUROCC) measurement was decreased in the patients with secondary sepsis compared with those without (AUROCC = 0.805, 95% confidence interval [CI]: 0.699–0.879, vs. 0.934, 95% CI: 0.881–0.970, respectively; $P < 0.050$). A cut-off of 2.0 ng/mL had a sensitivity of 83.3% in patients with primary sepsis but only 58% in patients with secondary sepsis. Moreover, the negative predictive value was much lower in the secondary sepsis, even if the 0.25 ng/mL threshold value was used.	[26]
	The potential role of PCT in diagnosis of intravascular catheter-related bloodstream Infections (CRBSI) in the ICU has been studied by Theodorou et al. PCT on the day of suspected infection (D0) was 7.70 and 0.10 ng/mL for patients with and without proven CRBSI, respectively ($P < 0.001$). The AUC for PCT was 0.990 (95% CI; 0.972–1.000), whereas a cut-off value of 0.70 ng/mL provided sensitivity and specificity of 92.3 and 100%, respectively. On the other hand, an increase >0.20 ng/mL of PCT between D0 and any of the four preceding days was associated with a positive predictive value exceeding 96%.	[27]
Ventilator-associated pneumonia (VAP)	Luyt et al. found that PCT levels from "before" to the day of VAP diagnosis, increased in 41% and 15% of patients with and without VAP, respectively. Thus, PCT had a good specificity (85%) but a low sensitivity (41%) for VAP diagnosis, with respective positive and negative predictive values of 68% and 65%.	[28]
	Ramirez et al. also evaluated the relationship between PCT levels and VAP. They established that a PCT level of 2.99 ng/mL had the best diagnostic cut-off (AUC 0.870, sensitivity 78%, specificity 97%, negative predictive value [NPV] 94%, positive predictive value [PPV] 87.5%). The combination of this cut-off of PCT with the simplified Clinical Pulmonary Infection Scores significantly improved the results (AUC 0.961, sensitivity 67%, specificity 100%, NPV 92%, PPV 100%) According to these results, PCT would avoid unnecessary antibiotic treatments by excluding false-positive diagnoses of VAP.	[29]
Lung transplant recipients	On the second postoperative day a PCT cut-off of 8.18 ng/mL has been shown to have an AUC of 0.97 (95%CI, 0.88-1.03, sensitivity 80%, specificity 100%, NPV 100%, PPV 95%) for the identification of infectious complications. On day 4 post-lung transplant, a cut-off of 2.63 ng/mL had an AUC of 0.88 (95%CI, 0.73-1.03, sensitivity 40%, specificity 100%, NPV 100%, PPV 82%).	[30]

7. Procalcitonin Use in Urinary tract infection

Urinary tract infection (UTI), particularly in older adults, is a leading cause of antibiotic use in acute care hospitals, outpatient clinics, and long-term care facilities [37]. Diagnosis of UTI is imprecise due to the lack of specificity in clinical and laboratory features. Differentiation of colonization and infection is impossible with urinalysis and culture alone because urine is not sterile and pyuria is common in asymptomatic patients [38]. Up to 60% of antibiotic prescriptions for UTI are considered unnecessary [39]. Given the harm associated with antibiotic overtreatment and the difficulty of identifying patients with invasive UTIs, researchers have explored the ability of biomarkers to guide treatment decisions for patients with urinary symptoms.

The utility of PCT in UTI has been extensively studied in children, but less so in adults. In paediatric patients, an elevated PCT was found to be a better predictor of acute pyelonephritis and renal scarring (as opposed to lower UTI) compared with CRP and leukocyte counts [40–49]. Precise cut-offs should be interpreted with caution as a more sensitive PCT assay was not used in these early studies. Elevated PCT values were also useful in detecting vesicoureteral reflux and avoiding cystography in children [50].

The use of PCT to guide antibiotic use in UTI in non-septic patients is limited to observational data, a single randomized trial, and expert consensus. In adults, observational studies have shown that PCT performs well for systemic infections. PCT values above >0.25 µg/L are associated with severe infections or ICU admission, higher 30-day mortality [51], and the presence of bacteraemia [52]. In a study of ED patients, PCT was observed to predict bacteraemic UTI at a threshold of 1.16 ng/mL, with an AUROCC of 0.993 [53]. Can PCT also detect localized UTI? Few studies have addressed this question in adults. An observational study of pregnant women noted that 30% of women with asymptomatic bacteriuria had an increase in serum PCT levels >0.05 ng/mL, whereas all women without bacteriuria had negative PCT levels [54].

Based on these observational data, Drozdov et al. conducted the randomized "triple p in UTI" study to evaluate PCT-guided treatment in lower and upper UTIs. As PCT has a higher sensitivity for systemic infections than localized infections, Drozdov et al. hypothesized that combining PCT with a marker of local urinary inflammation would improve its performance [55]. They randomized immunocompetent patients with non-catheter-associated UTIs to receive antibiotics based on clinical guidelines (controls) or with a PCT-pyuria-based algorithm (intervention). In the intervention arm, patients with uncomplicated lower tract infections received non-steroidal anti-inflammatory drugs (NSAIDs) only for 3 days. All other patients were treated with antibiotics. Outpatients with a PCT <0.25 ng/mL were treated with 3 days of antibiotic therapy, while those with values >0.25 ng/mL received 5-10 days depending on the PCT value (FIGURE 1). Inpatients underwent PCT and urinalysis testing every 2 days. Antibiotics were discontinued when PCT dropped below 0.25 ng/mL or PCT decreased by 80% and pyuria decreased by ≥90%. The duration of initial antibiotic therapy in the intervention group was 6 days compared with 10 days in the control group ($P < 0.001$). Overall there was no difference in adverse outcomes, which comprised mortality, persistent infection, recurrences, and rehospitalizations. However, 5 of the 9 bacteraemic patients in the intervention group experienced recurrent infection compared with only 3 of 19 patients in the control group (56% vs. 16%, P=0.04), which indicates caution is needed in this subgroup until larger studies validate this approach.

A more recent retrospective study conducted by Levine et al. evaluated whether PCT could be used to diagnose lower UTIs in adults who presented to an ED and underwent urinalysis and culture [56]. The study excluded patients with upper UTIs, pregnancy, immunocompromise, spinal cord injury and other conditions causing non-infectious elevations in PCT. Catheterized patients were

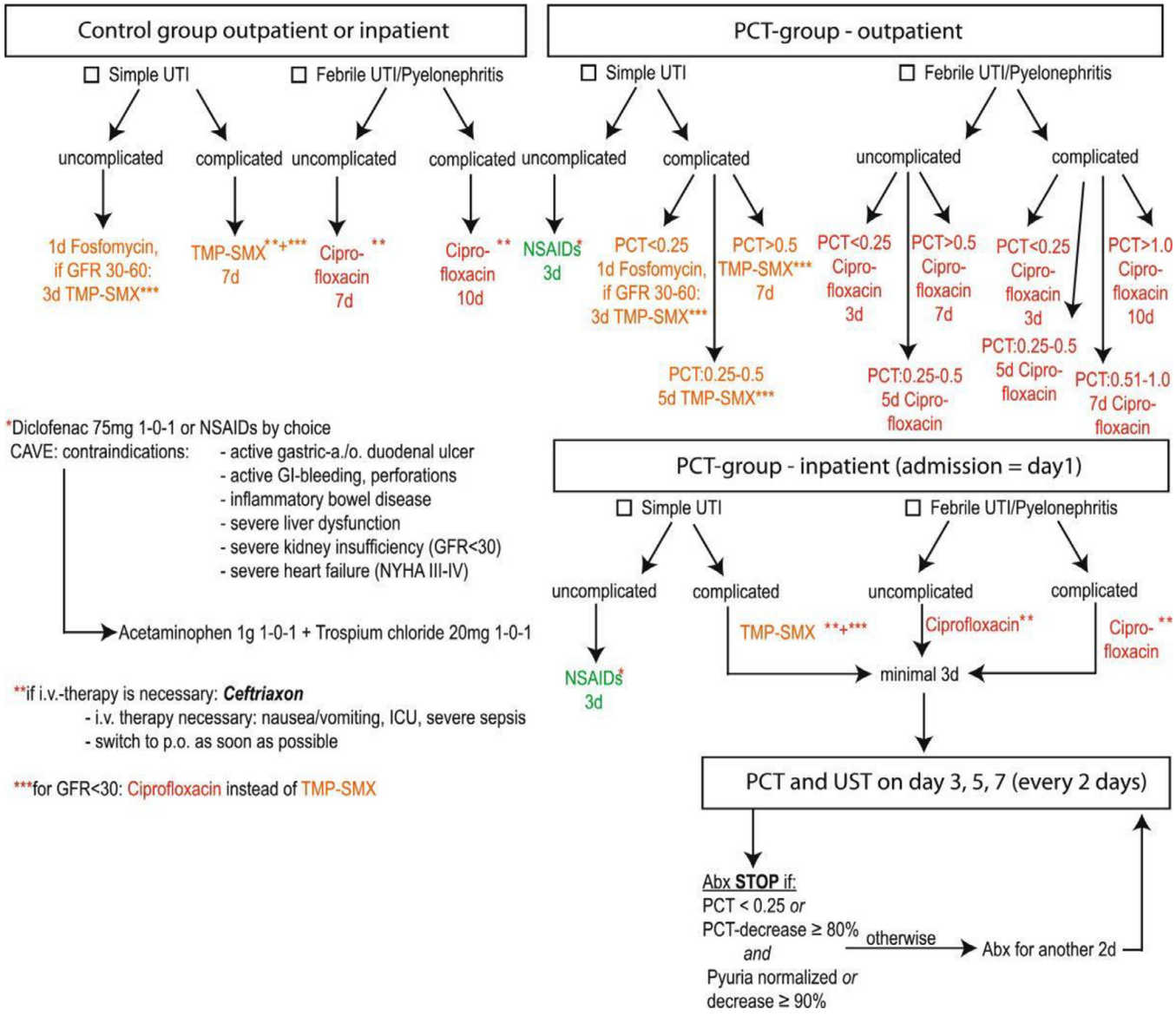

Fig. 1. Individualized antibiotic guidance by PCT and pyuria.
The algorithm for diagnostic purposes is shown. If there is any concern about microbiological resistance, extension of therapy is considered. For proven microbiological resistance, therapy is adjusted. Remaining antibiotic treatment after patient discharge is guided by the last PCT value to result in total antibiotic duration analogous to outpatient treatment. Abx: antibiotics; GFR: estimated glomerular filtration rate with MDRD formula; ICU: intensive care unit; NSAIDs: non-steroidal anti-inflammatory drugs; PCT: procalcitonin (in ng/mL); TMP-SMX: trimethoprim-sulfamethoxazole; UST: urinalysis; UTI: urinary tract infection. (From Drozdov et al, 2013 [55])

included. A "positive lower UTI diagnosis" was determined by retrospective chart review and defined as patients with lower urinary symptoms and a positive urine culture. Using these definitions, 48 patients were classified as positive (mean PCT=0.525 ng/mL) and 245 as negative (mean PCT=0.1 ng/mL). Using a threshold of <0.25 ng/mL, the AUROCC for predicting UTI was 0.717 (sensitivity 67%, specificity 63%, NPV 91%). This study supports the Drozdov approach of withholding antibiotics when the PCT is <0.25 ng/mL in lower UTIs, but the diagnostic accuracy is hampered by a retrospective approach and the lack of a coherent gold standard for UTI diagnosis. Further intervention studies are needed in catheterized patients and patients with spinal cord injury.

Despite limited evidence, PCT has been incorporated into clinical decision making for UTIs in numerous hospitals. In addition, a recent meeting of international experts, most of whom are members of the ISAC's Rapid Diagnostic and Biomarkers group, generated a set of consensus algorithms for PCT use in hospitalized patients, including those with UTI; these algorithms follow the same structure as those used in trials for lower respiratory tract infections [1]. Future studies should report on the outcomes of these programs and pathways so that UTI pathways can be further refined and validated.

8. Dynamics of CRP and PCT in infection in older populations

The elderly represent the fastest growing population, at least in the developed world. Advanced age is generally associated with a decline in immune function, commonly referred to as 'immune senescence', which makes this population more susceptible to infection, with potentially worse outcomes [57,58]. Physiological changes related to ageing, comorbidity, polypharmacy and geriatric syndromes might inhibit adequate response to infection, thereby reducing the prognostic accuracy of the clinical scores and biomarkers used in younger populations. Atypical clinical manifestations of infection in the elderly population, such as consciousness disturbance, lack of fever or irregular leucocytosis,

have been described and can make early diagnosis of infection in the elderly a major challenge for clinicians [59].

Diagnostic uncertainty can lead to frequent inappropriate initiations of antibiotic and longer durations of treatment [60] or underdiagnosis of sepsis, which may lead to a delay in therapeutic intervention and a poorer outcome. Hence, the use of biomarkers as diagnostic and/or stewardship tools is particularly important in older populations.

CRP and PCT are two of the most studied biomarkers [60]. The dynamics of CRP and PCT differ during bacterial infections, with an earlier increase of PCT and a shorter peak level phase when infection is under control [61]. However, these dynamics have not been clearly studied in elderly patients. There are contradictory reports regarding the sensitivity in localised infections in the elderly [59,60,62]. This can be attributed to: i) the high heterogeneity of studied populations and ii) the difficulties associated with determining or confirming localised infections. For example, UTI is sometimes defined by the presence of specific urinary tract clinical symptoms and signs with positive urine cultures; however, 30-50% of the older population exhibit bacterial colonisations and it is often difficult to reach a diagnosis in clinical practice [58]. Furthermore, interpreting chest X-rays for elderly patients presenting with respiratory symptoms can be a major challenge, leading to high inappropriate antibiotic use [63].

Despite those challenges, a meta-analysis including 4 studies showed that the AUROCC was 0.89 (95% confidence interval [CI]: 0.86–0.92). The overall sensitivity and specificity estimates for PCT tests were 0.83 (95% CI: 0.38–0.98) and 0.83 (95% CI: 0.60–0.94), respectively, for a cut-off of 0.5 ng/mL. The positive likelihood ratio for PCT (LR+ = 4.77; 95% CI: 2.49–9.13) was not sufficiently high as a rule-in diagnostic tool in the elderly. Nevertheless, it is a better diagnostic test compared with the low LR+ of CRP or WBC. The negative likelihood ratio for PCT was acceptably low for its use as a rule-out diagnostic tool (LR- = 0.20; 95% CI: 0.04–0.97) [59]. In addition, looking at systemic infections and bacteraemia, comparisons favoured PCT over CRP for its NPV of 95% in older populations at a cut-off of <0.5 ng/mL [64], confirming results of an earlier study with sensitivity for PCT of >90% and an NPV up to 95% for cut-off levels of 0.4 to 0.5 ng/mL [65]. Similar results were reported in a retrospective cohort of 776 blood cultures performed in older populations (>75 years old) in a single-centre study in France (Grenoble unpublished data).

PCT was measured as a stewardship tool in 55 patients aged 66-98 years with potential infections in a real-life setting. PCT was low (<0.25 ng/mL) in 39 of 55 patients. In conjunction with clinical findings, 64.1% of this group were not started on antibiotics and 20.5% had antibiotic treatment stopped. Four of the 39 (10%) who did not receive antibiotics as a result of low PCT died within 14 to 26 days. In contrast, in the high PCT group, 6 of 16 (40%) passed away and all were on antibiotics deemed to be appropriate for their condition [66]. To our knowledge there is only one randomized control trial, the PROPAGE study, that assesses the role of PCT in a decision-making PCT-based algorithm to individualise antibiotic duration, and PCT has resulted in reducing antibiotic duration in hospitalized elderly patients (>80 years old) with pneumonia (personal communication Gavazzi G, results unpublished).

Although PCT has a greater prognostic accuracy than CRP and WBC, it has lower prognostic value than MR-proADM and lactate in identifying patients with short-term mortality risk [67]. Moreover, the cut-off must be set-up to 1 ng/mL to achieve the best sensitivity and specificity.

In conclusion, different studies have shown that the performance of the PCT test in elderly patients is not inferior to that in other adult patients for diagnosis of infection and sepsis, but more studies are required to define best cut-off values and impact on outcome. For now, PCT or other markers should be used in combination with clinical scoring systems for decision making.

9. Procalcitonin and central nervous system infections

Early diagnosis and timely treatment of central nervous system (CNS) infections are crucial to avoid high mortality and neurological sequelae. Differentiation of bacterial meningitis (BM) from non-BM circumvents unnecessary hospitalization, unnecessary antibiotics, and cost [68]. However, this can be clinically challenging as features of BM and non-BM can be similar, particularly in newborns, the elderly, and immunosuppressed and diabetic patients.

Positive Gram-staining, bacterial culture or detection of bacterial antigens in the cerebrospinal fluid (CSF) represent the gold standard tests in BM diagnosis. However, despite high specificity, the sensitivity is poor [68], culture results, if any, could take 48-72 h and polymerase chain reaction (PCR) results may not be readily available. Furthermore, it is not always possible to obtain CSF samples.

Classic biological markers in blood (CRP, WBC, and neutrophil count) or in CSF when used alone do not offer high sensitivity and specificity for distinguishing BM and non-BM. Published data indicate that serum PCT is superior to traditional biomarkers for BM diagnosis within a clinical context. Different studies have reported serum PCT sensitivity and specificity ranging from 50% to 100% but there is still variation in choice of the “abnormal” cut-off values because of the diverse age range and nature of the study populations. BM should be diagnosed when the initial serum PCT is >0.25-0.5 ng/mL; however, serum PCT concentrations can decrease in 8-12 h with appropriate antibiotic treatment [68,69].

Although some studies have demonstrated that CSF PCT levels have a higher predictive value than serum PCT for diagnosis of BM, other studies indicate that serum PCT has a superior diagnostic value compared with CSF PCT among suspected BM patients [70]. It is currently not recommended to evaluate CSF PCT levels as a routine diagnostic test for BM [71]. Serum PCT must not be used to rule out BM, but to provide additional information to the clinical picture. Lactate level, CSF glucose−to−blood glucose ratio, and polymorphonuclear leukocytes in CSF as well as serum PCT have higher accuracy for BM diagnosis when used collectively [69]. The dynamic changes and trends of serum PCT in patients with BM can be used to evaluate the disease, guide the clinical medication, and monitor the prognosis [72]. Serum PCT has no role in diagnosis of focal bacterial CNS infections, brain abscesses and subdural empyema [73].

10. PCT in patients with neutropenic fever

Management of febrile neutropenic episodes is often a challenge because of a lack of microbiological and clinical documentation of infection. Investigation of the role of PCT in febrile neutropenia started almost 20 years ago and studies are small, with a wide range of sensitivity (42-72%) and specificity (64-89%), cut-off values of 0.5-0.8 ng/mL, and heterogenous populations [74]. A multicentre study of 158 febrile neutropenic patients reported sensitivity and specificity of PCT for bacteraemia of 44.2% and 64.3%, respectively, at concentrations of 1.0-5.0 ng/mL, and 83.3% and 100%, respectively, for severe sepsis at concentrations of >5.0 ng/mL [75]. Concentrations <0.5 ng/mL indicated that infection was unlikely, although bacteraemia associated with coagulase-negative staphylococci, an organism often associated with line-related sepsis, may fail to elevate serum PCT levels.

A more recent study prospectively evaluated the role of PCT in distinguishing infectious fever from non-infectious fever (NIF) among 108 febrile lymphoma patients [76]. Secondary objectives

were to evaluate the usefulness of PCT in distinguishing bloodstream infections (BSI), local infections unidentified infections (LIUI), and NIF. PCT was measured within 24 h of fever onset (PCT1) and 24-72 h later (PCT2). The higher PCT value between PCT1 and PCT2 was also documented (PCT_{max}). PCT levels (PCT1, PCT2, and PCT_{max}) were compared for BSI, LIUI, and NIF. In addition, the difference between PCT1 and PCT2 was evaluated in patients with complete data on both PCT1 and PCT2. PCT_{max} was statistically significantly different between the infectious fever (BSI and LIUI combined) and NIF groups (median PCT_{max}: 0.44 ng/mL vs. 0.19 ng/mL; P=0.026). PCT1 was not statistically significantly different for patients with BSI, LIUI, and NIF (P=0.217). However, PCT2 and PCT_{max} were significantly higher in patients with BSI compared with those with NIF (P=0.026 and 0.002, respectively). Meanwhile, patients with BSI have significantly higher PCT_{max} values than those with LIUI (P=0.034). Among 90 cases with complete data on both PCT1 and PCT2, PCT2 was statistically significantly higher than PCT1 in patients with BSI (median PCT: 0.98 ng/mL vs. 0.47 ng/mL; P=0.045) and patients with LIUI (median PCT: 0.43 ng/mL vs. 0.24 ng/mL; P=0.004) but not in patients with NIF (P=0.374). The authors concluded that two separate PCT measurements can differentiate between infectious fever and NIF and predict for BSI in lymphoma patients with fever.

Our working group suggests prompt and appropriate empirical antibacterial therapy in neutropenic patients, taking into account patients factors as well as microbiological and epidemiological data and local resistance patterns. We also encourage collaboration among centres that use PCT in febrile neutropenia to produce larger prospective, controlled studies to identify the real impact of PCT in these patients.

11. PCT and pancreatitis

The presentation of pancreatitis was one of the impetuses for establishing the systemic inflammatory response syndrome (SIRS) criteria. The initial presentation of pancreatitis is one of a sterile inflammatory response, which in some patients can become infected. PCT appears to have a role in identifying patients with an infected pancreas as well as prognosticating the severity of illness.

An animal model of pancreatitis in which sodium taurocholate was injected into the biliopancreatic duct disclosed two important outcomes that are potentially applicable to humans [77]. In this model, the development of pancreatic inflammation was associated with intestinal mucosal inflammation and translocation of bacteria. Additionally, measurements of PCT in both the serum and intestinal tissue correlated significantly with measurements of serum endotoxin and mucosal injury. These data indicate that PCT could be used to predict impairment of intestinal mucosal barrier function in induced pancreatitis. The distal nature of the inflammation caused by acute pancreatitis, particularly the involvement of the intestinal tract with the potential for translocation, may explain the strong systemic inflammatory response observed in pancreatitis.

Differentiation of pancreatic necrosis from infection is a clinical challenge. In one study, researchers followed patients with pancreatic necrosis to see whether or not they developed pancreatic infection [78]. Pancreatic necrosis was diagnosed using computed tomography (CT) contrast-enhanced criteria, whereas pancreatic infection was diagnosed using fine-needle aspiration and culture of the pancreatic necrosis in all study patients. An elevated PCT identified the patients with infected necrosis with an AUC >0.77 and was superior to other biomarkers of inflammation. Combining PCT with the other biomarkers improved the receiver-operating characteristic (ROC) even further.

Ramon Sager et al. reviewed data evaluating PCT as an antibiotic stewardship tool in pancreatitis [79]. The authors reported a randomized controlled trial of 71 patients with pancreatitis that showed PCT could be used to reduce antibiotic exposure compared with routine prophylactic antibiotic usage in patients with pancreatitis.

Few studies have evaluated the sensitivity and specificity of PCT for distinguishing sterile and infected pancreatic injury. The studies that have been published are small but are generally positive.

The role of PCT as a marker of severity of pancreatitis has been evaluated. In a study reported in Pancreas [80], PCT was compared to standard scoring systems to predict the severity of pancreatitis. A PCT level >0.5 ng/mL had the best ROC characteristics, with an AUC of 0.78; this was followed by Ranson's Criteria with a score ≥3 (AUC 0.76), APACHE II score ≥8 (AUC 0.72), BISAP score ≥3 (AUC 0.66) and CT severity index score ≥3 (AUC 0.53). These data were virtually duplicated by Lee et al., who demonstrated that PCT has the best predictive value, with the only difference being that CRP2 was also used as a biomarker. Lee's study also showed that PCT could discriminate between mild, moderate and severe pancreatitis, which could lead to more appropriate resource allocation for patients.

An important characteristic of a good biomarker is the ability to rapidly identify the pathological process. PCT and CRP response rates were compared in a study of severe acute pancreatitis [81]. PCT rose to its peak level by 24 h whereas CRP levels peaked at 72-96 h after symptom onset. Within 36 h of initial symptoms a PCT ≥0.5 ng/mL had an 81% sensitivity and 86% specificity for acute pancreatitis. In addition, plasma PCT levels, but not CRP or WBC, correlated significantly with ICU requirement.

The above results differ from those reported by Modrau et al. [82] where PCT was less predictive than standard measures but in this study, there were significant time differences with respect to the measurement of biomarkers. IL6 release occurs earlier than PCT and CRP release and is associated with an acute inflammatory response and release of other inflammatory mediators but has not been sufficiently tested to determine its utility in severe acute pancreatitis.

A study of 104 patients with predicted severe acute pancreatitis in five European academic surgical centres measured PCT within 96 h of symptom onset [83]. CRP was routinely assessed and both biomarkers were monitored over a maximum of 21 consecutive days and in weekly intervals thereafter. In contrast to CRP, PCT concentrations were significantly elevated in patients with pancreatic infections and associated multiorgan dysfunction syndrome (MODS) who all required surgery (n=10) and in non-survivors (n=8) early after onset of symptoms. PCT levels were only moderately increased in patients with pancreatic infections in the absence of MODS (n=7), all of whom were managed non-surgically and survived. A PCT value ≥3.5 ng/mL on 2 consecutive days was superior to CRP ≥430 mg/L for the assessment of infected necrosis with MODS or non-survival, as determined by ROC analysis with a sensitivity and specificity of 93% and 88% for PCT and 40% and 100% for CRP, respectively (P < 0.01). The single or combined prediction of the two major complications was already possible on the third and fourth day after onset of symptoms with a sensitivity and specificity of 79% and 93% for PCT ≥3.8 ng/mL compared with 36% and 97% for CRP ≥430 mg/L, respectively (P=0.002).

In conclusion, PCT appears to enable identification and prognostication of infective complications of pancreatitis; however, these conclusions are based on only a few small studies and further research is warranted.

12. Role of procalcitonin in diagnosing musculoskeletal infection

Studies assessing the role of PCT for the diagnosis of localised skin infections have been small and heterogenous and have shown

mixed results [84]. Data from the clindamycin for cellulitis trial [85] indicated serum PCT was not helpful whereas Rast et al. [86] demonstrated that PCT was significantly higher in patients with cellulitis compared with those with deep vein thrombosis. A much lower PCT cut-off (>0.1 ng/mL) was required to increase its sensitivity. Al-Thani et al. [87] showed that serum PCT was a useful prognostic marker in necrotising fasciitis, and two further studies [86,88] found PCT increased with the severity of skin infection. Serum PCT has not so far been demonstrated to aid the diagnosis of localised skin infections, although it may be used as a prognostic marker in severe skin infections, including necrotising fasciitis. The clinical uncertainty and significant diagnostic error associated with cellulitis make biomarker studies challenging to interpret. Prospective randomized trials of PCT-guided antibiotic therapy are needed.

Three of six studies reported that PCT was higher in patients with an infected diabetic foot ulcer (IDFU) compared with patients with a non-infected DFU [89–91]. The cut-off had to be lowered (0.08-0.2 ng/mL) to show significance. These three studies used a quantitative assay with a lower assay range. The other three studies reported PCT to be unhelpful in diagnosing IDFU, but may have used a less sensitive method to measure PCT [92–94]. These results indicate a quantitative assay with a lower assay range may enable PCT to be a useful biomarker in IDFU.

Serum PCT was found to be higher in septic arthritis compared with non-infective arthritis in several studies [90,95–104]; however, it is yet to be proven as a useful biomarker for septic arthritis in prospective studies. Using a PCT cut-off of 0.5 ng/mL has a high specificity, but the sensitivity, although variable, was too low to be useful in clinical practice. Synovial fluid PCT results have been inconclusive: some studies [91,92] found it to be more sensitive than serum PCT, and others [93,94] failed to demonstrate any significant difference between septic arthritis and non-infective arthritis synovial fluid PCT levels. Again, all sample sizes were small, the comparison groups differed between studies and a range of PCT assays with differing sensitivity were used; therefore, it is difficult to directly compare studies.

There are limited studies analysing PCT in osteomyelitis (OM). Studies have shown a significantly higher serum PCT in acute OM in children compared with healthy controls [95] and in OM associated with diabetic foot ulcers compared with those without OM [97]. There is little evidence thus far to support its use in the general population.

13. Newborn sepsis and PCT

PCT is not as widely investigated in newborns and children as it is in adults. Levels of PCT have been shown to increase within 4 h in neonates during the sepsis process, reaching peaks in 6-8 h. In normal-birth-weight neonates, a PCT cut-off limit >0.5 ng/mL indicates a two-fold probability of neonatal sepsis and a cut-off >2.4 ng/mL gave a PPV of neonatal sepsis near to 50%, with a probability of a false-positive diagnosis of neonatal sepsis in about 10% of the patients [105].

A multinational, randomised controlled trial was conducted in which neonates of gestational age of at least 34 weeks with suspected early-onset sepsis requiring antibiotic treatment were randomly assigned to PCT-guided therapy (n=866) or standard therapy (n=844) [106]. A total of 1408 neonates underwent per-protocol analysis (745 in the PCT group and 663 in the standard group). The duration of antibiotic therapy for the PCT group was reduced (intention to treat: 55.1 vs. 65.0 h, $P < 0.0001$; per protocol: 51.8 vs. 64.0 h; $P < 0.0001$). There were no sepsis-related deaths, and <1% of neonates had possible re-infection. The authors concluded that PCT-guided decision making was superior to standard care in reducing antibiotic therapy in neonates with suspected early-onset sepsis. Non-inferiority for re-infection or death could not be shown due to the low occurrence of re-infections and absence of study-related death.

A small, prospective study on a neonatal ICU involving 50 newborns with no control group investigated PCT as an early sepsis marker. The authors concluded that low (<0.5 mM/L) levels of PCT made systemic infection unlikely, a PCT of 0.5-2.0 mM/L was associated with mild infection and a PCT of 2–10 mM/L was considered to be moderate, reflecting a very likely systemic infection with high risk for progression to severe systemic infection. A PCT >10 mM/L was associated with possible systemic inflammatory response most likely due to severe bacterial sepsis with high likelihood of severe sepsis [107].

In a recent meta-analysis and systematic review, Ruan et al. compared the diagnostic accuracy of PCT, CRP, PCT + CRP and presepsin in the diagnosis of neonatal sepsis from 28 studies involving over 2600 patients [108]. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), AUC, and corresponding 95% CI were the primary outcomes. Secondary outcomes included the sensitivity and specificity in multiple subgroup analyses. The pooled sensitivity of CRP (0.71 [0.63, 0.78]) was weaker than that of PCT (0.85 [0.79, 0.89]), PCT + CRP (0.91 [0.84, 0.95]) and presepsin (0.94 [0.80, 0.99]); the pooled NLR of presepsin (0.06 [0.02, 0.23]) and PCT + CRP (0.10 [0.05, 0.19]) were less than that of CRP (0.33 [0.26, 0.42]); and the AUC for presepsin (0.99 [0.98, 1.00]) was greater than that of PCT + CRP (0.96 [0.93, 0.97]), CRP (0.85 [0.82, 0.88]) and PCT (0.91 [0.89, 0.94]). The results of the subgroup analysis showed that 0.5-2 ng/mL may be the appropriate cut-off interval for PCT. The authors concluded that combination of PCT and CRP or presepsin alone improves the accuracy of diagnosis of neonatal sepsis. However, further studies are required to confirm these findings.

Like any other tests, PCT has limitations in this age group. Studies in term infants showed a physiological rise in PCT concentration during the first 48 h of life, with a peak of 20 ng/mL at 24 h. Apart from those proven cases where PCT was elevated due to bacterial infections, some neonates demonstrated an increased level of PCT when hypoglycaemia or respiratory distress was diagnosed without bacterial infection. This has provoked debate on whether PCT can be used in newborns as an indicator of bacterial infection or sepsis [109].

Diagnosis of neonatal sepsis remains challenging. There is a major need for improved diagnostics to help better identify those infants requiring immediate parental antibiotics from those who do not. Point-of-care PCT and other novel markers need to be further investigated in this age group.

14. Conclusion

PCT has shown great promise for risk stratification of patients and individualization of antibiotic treatment, with an overall reduction in antibiotic exposure leading to reductions in side effects and improvements in clinical outcomes. PCT measurements should always be interpreted in consideration of the overall assessment of each patient. In addition, these measurements should never delay the initiation of treatment in high-risk patients and critical states. However, PCT measurements can be used to monitor resolution of infection and help define the length of treatment. Despite the promising results mainly from patients with sepsis and respiratory infections, further trials are needed for other settings and types of infections highlighted in this review to optimise the use of PCT.

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