



A 2020 review on the role of procalcitonin in different clinical settings: an update conducted with the tools of the Evidence Based Laboratory Medicine

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Abstract: Biomarkers to guide antibiotic treatment decisions have been proposed as an effective way to enhancing a more appropriate use of antibiotics. As a biomarker, procalcitonin (PCT) has been found to have good specificity to distinguish bacterial from non-bacterial inflammations. Decisions regarding antibiotic use in an individual patient are complex and should be based on the pre-test probability for bacterial infection, the severity of presentation and the results of PCT serum concentration. In the context of a high pre-test probability for bacterial infections and/or a high-risk patient with sepsis, monitoring of PCT over time helps to track the resolution of infection and decisions regarding early stop of antibiotic treatment. As outlined by the Evidence Based Laboratory Medicine (EBLM), not only the pre-test probability but also the positive likelihood ratio influence the performance of a test do be really diagnostic. This aspect should be taken into account in the interpretation of the results of clinical trials evaluating the performance of PCT in guiding antibiotic therapy.

Keywords: Procalcitonin (PCT); Evidence Based Laboratory Medicine (EBLM); antibiotic therapy

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In the bid towards a more appropriate use of antibiotics, biomarkers have been found to be an effective support to clinicians in their antibiotic treatment decisions. As a biomarker, procalcitonin (PCT) is valued for its specificity in differentiating between bacterial and non-bacterial inflammation and is considered of utility to avoid unnecessary antibiotic prescriptions as well as to reduce the duration of antibiotic therapy (1). The aim of this paper is to review PCT use in different clinical settings and patient populations with a focus on trials and meta-analysis published between 2010 and 2019, in order to consider

reagents and analyzers that are still used in laboratories and interpreting the collected data with the Evidence Laboratory Medicine tools (2-4).

PCT in infected critically ill patient

The use and usefulness of PCT as a biomarker is covered extensively in literature in two main areas: as an early marker of sepsis (differentiating bacterial and non bacterial etiologies) and as a guide to the management of antibiotic therapy (5-20). In recent decades, there has been a shift

in the focus on PCT as a biomarker able to guide the discontinuation of antibiotic therapy, particularly in critically ill patients (5,7,9,10,12-16,18), demonstrating its safety and efficacy either alone or in association with other biomarkers, such as C-reactive protein (CRP), alpha 2 macroglobulin (A2M) and presepsin (19,21,22).

PCT has been compared with CRP to guide antibiotic therapy in septic patients, resulting equally effective in reducing antibiotic use (22). A recent review provided evidence that the diagnostic accuracy of PCT and presepsin to detect infections in critically ill adults was similar, without significant differences both in pooled sensitivity ($P=0.48$) and specificity ($P=0.57$) (5). The combination of A2M and PCT (collected at baseline and after 72 hours) achieved a negative predictive value (NPV) of 75% (95% CI, 54–96%) and was able to discriminate between bacterial sepsis and other causes of systemic inflammatory response syndrome (SIRS) in patients with suspected post-surgical sepsis (21). Conversely, in other trials the real efficacy provided by PCT in guiding the clinician's diagnosis has been questioned (7,8,10,11,19,23). Jeon *et al.* (9) confirmed the role of PCT as a biomarker capable of reducing the duration of antibiotic treatment, but found that its use did not impact on clinical cure, 28-day mortality, in-hospital mortality, ICU length of stay and overall hospital length of stay, when comparing the PCT-guided and the control group of patients. Pepper *et al.* evaluated the PCT-guided antibiotic discontinuation approach in a systematic review including 16 randomized clinical trials (RCTs) (23); they found that this approach was associated with decreased mortality (risk ratio, 0.89; 95% CI, 0.83–0.97) and with a decrease in antibiotics' duration (mean difference, 1.31 days; 95% CI, –2.27 to –0.35). They also found low-certainty evidence to support this PCT's clinical use, concluding that it was difficult to attribute the survival benefit to a PCT-guided approach as the reported examples were from studies where the protocol was not always strictly observed (i.e., investigators frequently overruled PCT guidance) or in which PCT were associated with other biomarkers (CRP) (23).

Two recent papers investigated the cost-effectiveness of PCT-guided antibiotic discontinuation in The Netherlands, a country that has a tradition of a low rate of antibiotic prescription both in the hospital setting and in the community (24,25). Kip *et al.* showed that a PCT-based algorithm for antibiotic discontinuation in ICU adult patients is safe and offers a cost-effective means of reducing antibiotic exposure (24). The same authors compared cost-

effectiveness of PCT testing and no-PCT testing in guiding antibiotic treatment duration in critically ill patients (25). Despite a mean lower course duration of antibiotics in the PCT-guided group, healthcare costs over a one-year time target were €73,665/patient compared with €70,961/patient in the standard of care group, with a modest impact of PCT's use on total healthcare-related costs (25). They concluded that the long-term cost-effectiveness of PCT guidance needs more studies, also in countries characterized by different antibiotic consumption if compared to The Netherlands (25).

PCT in lower respiratory tract infections

Pneumonia and acute respiratory infections (ARI) are a major cause of morbidity and mortality and ARI encompasses heterogeneous group of both bacterial and viral infections. Prompt intervention in terms of antibiotic treatment is crucial for the effective treatment of bacterial ARIs and is considered key to improve clinical outcomes; however, the etiologic diagnosis is not always achieved. Furthermore the overuse of antibiotics for acute respiratory syndrome [outpatients with bronchitis, prolonged antibiotic therapy in people with bacterial ARIs in hospital and intensive care unit (ICU)] is associated with the increase of multi-drug resistant bacteria, higher costs and adverse drug reactions (26).

PCT appears to be particularly sensitive to bacterial toxins compared to other biomarkers such as white blood cells (WBC) and CRP, and it undergoes down-regulation in the presence of viral infections. In 2017 PCT was approved as a marker to guide antibiotic therapy in lower respiratory tract infections, by the US Food and Drug Administration but, despite this step, there is no consensus about the usefulness of this marker to guide antimicrobial therapy in the currently available international guidelines for the management of pneumonia. The role of PCT in ARI has been studied in RCTs considering different settings (ICU; outpatients), to address when antibiotics should be initiated and when they should be interrupted. Many studies evaluated the use of PCT as part of a flow-chart, but one of the main obstacles they met was the definition of a standardized and accepted cut-off level. Most studies agreed to begin the antimicrobial therapy as follows: PCT <0.1 ng/mL strongly discouraged, PCT <0.25 ng/mL discouraged, PCT >0.25 ng/mL encouraged, PCT >0.5 ng/mL strongly recommended (12).

Some recent RCTs investigated if the use of PCT might be associated with improved antibiotics prescription.

Huang *et al.* (27) involved 1,656 patients with suspected lower respiratory tract infection and found that antibiotic treatment decisions based on PCTs did not lead to a reduction in the use of antibiotics when compared with standard care. The authors reported that while in some cases they discontinued antibiotics on the basis of PCT levels, they also used this biomarker to prescribe antibiotics in the PCT-guided group. Christ-Crain *et al.* (28) conducted a study involving patients affected by suspected community-acquired pneumonia (CAP) presenting to the emergency department. The therapy was oriented by a PCT-based algorithm in 151 patients, whereas other 151 received standard approach. In the case of the first group, the result was a reduction of antibiotic prescription (both total antibiotic exposure and duration: 5 versus 12 days). Briel *et al.* (29) conducted a multicenter RCT in primary care involving 458 patients who required antibiotics: these patients were randomized to either PCT-guided therapy (antibiotics strongly discouraged if PCT ≤ 0.1 ng/mL or encouraged if >0.25 ng/mL) or a standard approach. In the PCT-group, the overall antibiotic prescription rate was 72% lower and the treatment's duration was also found to be 1 day shorter; adverse events were the same for both groups. Akagi *et al.* (30) found that using a PCT-guided antibiotic discontinuation algorithm, the duration of antibiotic treatment is shortened by 3 days without any impact on pneumonia recurrence or 30-day mortality.

Schuetz *et al.* (26) conducted a systematic review to assess the safety and efficacy of PCT to start or interrupt antibiotics over a large range of patients with varying severity of ARIs and from different clinical settings. The results showed a significantly lower mortality associated with PCT-guided therapy, with a shortening of antibiotic treatment of 2.4 days and lower risk of antibiotic-related side effects. The systematic review and meta-analysis by Kamat *et al.* (31) suggest that PCT is unlikely to provide information that will enable clinicians to immediately address whether a CAP is bacterial, and antibiotics need to be administered, or whether it is viral, and antibiotics may be withheld. The sensitivity (overall 55%) and specificity (76%) were both too low and variable for the results to be confidently used in the decision-making process. The calculated LR+, LR- and DOR are respectively 2.3, 0.4 and 3.9, resulting inadequate for an effective diagnostic test. Finally, in a recently published review made by Creamer *et al.* (32), the authors' conclusion was that there are no recommendations for using PCT in managing CAP and that there is only one circumstance where PCT-guided therapy

is validated by international guidelines, namely in complex hospital-acquired or ventilator-associated pneumonia.

PCT in chronic obstructive pulmonary disease (COPD)

COPD is one of the most important causes of morbidity and mortality worldwide (33) and acute COPD exacerbations (AECOPD) represent a major health concern because of the progressive worsening of clinical condition (34). Clear criteria do not exist to distinguish an AECOPD from a daily respiratory variation. Furthermore, there is a lack of understanding regarding the AECOPD's pathogenesis: infective causes would be involved in 50% cases (35). Therefore, for an adequate management of AECOPD, antibiotics could be necessary but it is difficult to discriminate infectious from non-infectious episodes and antibiotic overuse can promote the onset of resistance and increase adverse reactions (27). Global Initiative for Obstructive Lung Disease (GOLD) recommendations suggest antibiotics when the patient presents at least two of the three cardinal symptoms (dyspnea, increased sputum production and purulence) or in presence of severe respiratory impairment (36).

Over the years, many researchers have attempted to identify a biomarker that goes beyond the clinical presentation and that would allow physicians to act more confidently. Compared to WBC and CRP, PCT has proven to be a more specific parameter of infections (32), and some authors have studied a PCT-guided algorithm as a useful tool to lead physicians to smart antibiotic therapies in patients affected by COPD. Generally speaking, all the cited studies (27,32-45) have tried to address the same questions: can PCT orient medical decisions? Can a PCT-guided algorithm show when antibiotics are necessary and when they are not, thus maintaining efficacy and safety? Can this strategy be also cost-effective? Despite the efforts, there is still insufficient evidence to draw solid conclusions. Firstly, there is no agreement about the real usefulness of PCT. According to Ni *et al.* (37), PCT has a moderate ability to identify bacterial respiratory infections in AECOPD, but does not have a strong diagnostic value in patients admitted in ICU. Lin *et al.* (34) concluded that PCT-guided treatment reduces the abuse of antibiotics, but Verduri *et al.* (38) were not able to demonstrate the non-inferiority of PCT-guided antibiotic treatment compared to standard treatment and Daubin *et al.* (35) came to the same conclusion. Moreover, even if PCT can

be useful together with symptoms and other biomarkers, a universal cut-off has yet to be defined. In Mathioudakis *et al.* (39) some studies used a cut-off ≥ 0.25 ng/mL to recommend antibiotics; Li *et al.* (40) considered values between 0.1 and 0.25 ng/mL and van der Maas *et al.* (41) values greater than 0.5 ng/mL to orient medical decisions. Furthermore many studies are flawed because of the low adherence to the protocols (32,42); according to van der Maas *et al.* (41), a PCT-guided algorithm seems to be more cost-effective than the current practice.

PCT in acute infections of central nervous system

Acute meningitis is classified into bacterial meningitis (BM) and nonbacterial meningitis. It can be extremely challenging to diagnose patients with BM, particularly because the clinical distinction between viral meningitis (VM) and BM is complex especially in the acute phase. The positivity of cerebrospinal fluid (CSF) culture, or Gram staining or the detection of bacterial antigens in the CSF, constitute the gold standard in BM diagnosis. They have high specificity but sensitivity is poor. Furthermore, bacterial culture is time-consuming. Therefore, in some cases, antibiotics are administered while waiting for CSF results or until a diagnosis of VM can be confirmed (46).

Biomarkers such as CRP and WBC help in distinguishing between BM and VM; however, neither of these tests achieve 100% sensitivity (47-49). CRP, traditionally a biomarker for inflammation, may show a delayed increase during a bacterial infection, resulting in false-negative results in the early stages of the disease (50-52). CRP can also be elevated in viral infections, limiting its ability to discriminate between bacterial and viral etiologies (53), and more sensitive and specific markers for BM are desirable (54).

In an observational study by Alkhali *et al.* (55), patients with BM were found to have increased serum PCT compared with the control group ($P < 0.001$) at the time of diagnosis. Similarly, when comparing patients with BM and VM, the first was found to have increased serum PCT at the time of diagnosis (PCT, $P < 0.001$). PCT level in VM cases is not so high which means that it is more accurate than CRP as a marker of systemic bacterial infection (56-58).

In terms of diagnostic cut-off levels, optimum sensitivity and specificity were calculated to be PCT > 10 ng/mL; a PCT > 2 ng/mL had 100% sensitivity and high NPV for BM, but with a specificity of only 60% and positive

predictive value of 68%. Follow-up of cases showed a significant reduction in PCT levels on the third day after antibiotic treatment initiation. This result is documented in many studies (59,60) and as such PCT can be considered a parameter for evaluating the efficacy of antibiotic treatment.

In 2015 a meta-analysis (61) including nine studies (62-70) demonstrated that serum PCT was a highly accurate test for diagnosing meningitis. The pooled sensitivity, specificity, LR+, LR-, and DOR for PCT were 0.90 (95% CI, 0.84-0.94), 0.98 (95% CI, 0.97-0.99), 27.3 (95% CI, 8.2-91.1), 0.13 (95% CI, 0.07-0.26), and 287.0 (95% CI, 58.5-1,409.0), respectively. PCT was found to be far superior to CRP, which had a pooled DOR of only 22.1 (95% CI, 12.7-38.3). For PCT the area under the curve (AUC) was 0.97 (standard error = 0.03). This analysis demonstrated that serum PCT was a highly accurate diagnostic test for distinguishing between bacterial and viral or non-infective etiologies in patients with suspected meningitis.

Furthermore, PCT was found to be more specific than sensitive. For this reason, the authors concluded that it would be opportune to use it in association to the traditional approach which considers the clinical history, physical examination, laboratory tests, and CSF analysis. This, with a view to increasing the overall diagnostic accuracy in differentiating the etiology of suspected meningitis. Considering its high sensitivity and specificity, PCT would be of added value in cases where conventional tests are unable to reach a conclusive diagnosis (i.e., non-conclusive CSF findings).

Another meta-analysis by Wei *et al.* (54) included twenty-two studies to ascertain the diagnostic accuracy of blood and CSF-PCT as a marker for BM detection (49,55,56,62-65,68-82): overall, the diagnostic sensitivity of CSF-PCT detection was 0.80 (95% CI, 0.61-0.91), specificity was 0.86 (95% CI, 0.70-0.95), LR+ was 5.9 (95% CI, 2.4-14.0), LR- was 0.23 (95% CI, 0.12-0.47), and DOR was 25 (95% CI, 8-78). The diagnostic sensitivity of blood PCT detection was 0.95 (95% CI, 0.89-0.97), specificity was 0.97 (95% CI, 0.89-0.99), LR+ was 31.7 (95% CI, 8.0-124.8), LR- was 0.06 (95% CI, 0.03-0.11), DOR was 568 (95% CI, 103-3,141). The AUCs for CSF-PCT and blood PCT were 0.90 (95% CI, 0.87-0.92) and 0.98 (95% CI, 0.97-0.99), respectively. The 95% CIs for the AUCs of CSF-PCT and blood PCT did not overlap, indicating that the overall diagnostic accuracy of blood PCT detection was superior to CSF-PCT. In particular, their results indicated that positive blood PCT could confirm a diagnosis of BM, while negative

blood PCT alone is sufficient to rule out it.

More recently, a cross-sectional study evaluated lactate, PCT, ferritin, CRP, and other known biomarkers in differentiating BM from VM and it found really opposite results because concentrations of all markers were significantly different in the two groups, except for blood and CSF-PCT. The mean CSF-PCT levels in patients with bacterial and viral/aseptic meningitis were 0.6 and 0.5 ng/mL, respectively ($P=0.136$); the mean serum PCT levels were 0.7 and 0.6 ng/mL in bacterial and viral/aseptic groups respectively ($P=0.389$). Using a cut-off of 0.4 ng/mL, CSF-PCT had poor sensitivity (75%), specificity (47%), LR+ (1.4), LR- (0.7) and DOR (2.7); using a cut-off of 0.6 ng/mL, serum PCT had sensitivity of 66.7% a specificity of 59.3%, with 1.6 LR+, 0.6 LR- and 2.9 DOR (83). They concluded that both CSF and serum PCT were weak marker in differentiating BM and VM.

PCT in infectious complications of polytrauma

Trauma is the principal cause of death in adulthood (>40 years of age) and the third leading cause of death overall (84,85). The management of patients with polytrauma can be complex and the clinical course can be fraught with complications, leading ultimately to mortality (86); death can occur immediately after injury (45% of cases), within the first day (10%) (brain injury or uncontrolled haemorrhage) and in the following days (45%) as a result of major complications [sepsis, respiratory distress syndrome and multiple organ failure syndrome (MOF)] (87). Sepsis is the main cause of late death (>1 week) because of an up regulation of anti-inflammatory agents and consequent energy that can precipitate patients in septic MOF (87-92).

Early diagnosis and treatment of infection is associated with improved outcome and reduced mortality (93), but the diagnosis of septic complications in major trauma is challenging as trauma per se provokes a strong SIRS that can mask clinical symptoms associated with sepsis (88-92). Bacterial culture is the standard in diagnosing the pathogen during sepsis (94) but immediate positive bacterial culture results are often unavailable and new rapid-diagnosis techniques are not always available in routine clinical practice (95).

Recently, two meta-analyses considered biomarkers predicting sepsis in polytrauma patients (96,97). Ciriello *et al.* (96) showed that PCT has rapid kinetics, with levels peaking at 24-48 h after trauma and rapid decrease in non-

complicated patients (98-102). Persistent high levels or secondary increases were adequate predictors of sepsis (98-101,103-106), and MOF (100,103,106-108). The authors found PCT to be useful in predicting septic course and in allowing early diagnosis of MOF and of significant infective complication. However, by the same token, the authors pointed out that sensitivity and specificity reported for PCT at the different cut-off levels meant that it could not be used as a single indicator of sepsis and that the trend of PCT, as opposed to a single value, was the best tool to indicate infective complications.

AlRawahi *et al.* (97) identified 19 studies (4,146 patients), many of them in common with Ciriello. Most studies showed rapid kinetics of PCT levels with peak levels reached 1 day after trauma (98-106,108-112), and to a lesser extent on day 2 (113,114). Two studies demonstrated that a biphasic rise in PCT after one week was associated with development of sepsis (98,114). Nine studies (47.4%) (99,100,102,106-110,112) investigated the correlation between initial PCT level and the severity of trauma using injury severity score (ISS) (115): at the beginning PCT was higher in case of severe trauma ($ISS >20$) (99,102,106,110). Sixteen studies (84.2%) assessed the value of PCT level as a marker for sepsis (98-109,111,114,116,117). After reaching the peak level on day 1 after trauma, PCT declined immediately towards reference interval (98,102-104,106). However, the peak was significantly higher in patients who subsequently developed sepsis compared to those without sepsis (98,100,102-107,109,110). Furthermore, patients who developed sepsis demonstrated a significant increase of peak PCT levels compared with patients with non-infectious SIRS (98,99,101,106). Furthermore seven studies demonstrated significantly higher initial PCT levels in patients who subsequently developed multi organ dysfunction (MOD) compared to those without MOD (100,101,105,106,108,112,114).

PCT in infectious complications of burns

Severe burn injuries are a major insult: tissue injury, with the release of multiple local and systemic mediators of inflammation, determines an increased vascular permeability resulting in significant hydro-electrolytic and cardiovascular alterations (118), rapidly evolving to shock. In the past, shock was the primary cause of death in burn patients. However, thanks to advances in intensive care, this is no longer the case (119). Today, sepsis is the leading cause of death in this type of patient, occurring

generally in a late post-traumatic period (119,120). Early diagnosis of sepsis is crucial for the management and outcome of critically burned patients. Nevertheless signs of infection may be obscured by systemic dysfunction. All burns >15–20% of total body area surface (TBSA) have a SIRS that persists for months after the wound is closed, so that at baseline burn patients always have the signs used to diagnose sepsis in the general population (121). To improve clinical criteria for sepsis detection in burned patients, members of the American Burn Association suggested the modification of some cut-offs of the SIRS parameters and the concomitant documentation of infection (122). Notwithstanding the above, it can still take quite a few days before microbiological agents can be identified conclusively (123).

PCT has been proposed as a biomarker to early identify a septic process and to select burned patients for prompt antibiotic therapy. Moreover, when PCT levels are under the cut-off values defined for septic processes, it may suggest antibiotic discontinuation, also becoming useful to avoid unnecessary therapy. In a systematic review by Mann *et al.* (124), two meta-analyses resulted in differing conclusions. The diagnostic odds ratio (OR) of PCT to diagnose sepsis reported by Jones *et al.* (125) was 9.86 (95% CI, 5.72–17.02), in contrast with Tang *et al.* (126) for which an OR of 7.79 (95% CI, 5.86–10.35) was calculated for the ability of this test to accurately discriminate between sepsis and non-septic SIRS. Mann *et al.* concluded that utility of the PCT assay is limited due to the lack of availability of rapid, inexpensive tests. In the same systematic review, six clinical trials conducted on burn injured patients were also retrieved (127–132). In burn specific studies, varying cut-off levels of PCT were observed, namely: from 0.5 ng/mL (sensitivity 100% and specificity 89.8% for diagnosis of sepsis) (127) and 0.53 ng/mL (sensitivity 42.4% and 88.8%) (128) to 3.0 ng/mL associated with septic complications (130). Sachse *et al.* (132) reported a 1.5 ng/mL rise in daily PCT levels simultaneously with a septic event. There was no improvement in detection of sepsis using PCT compared with CRP in a study of pediatric burn patients (131). Lavrentieva *et al.* (129) found the PCT cut-off level of 1.5 ng/mL to have the highest sensitivity (82%) and specificity (91.2%) in septic patients (7.7 LR+ and 0.13 LR–), and found a sensitivity of 88% and specificity 92.2% considering a PCT cut-off of 1.5 ng/mL in case of wound infection (11.5 LR+, 0.2 LR–); in burn patients with respiratory tract infection a PCT cut-off of 0.56 ng/mL showed respectively 75%

sensitivity, 80% specificity, a LR+ of 4 and a LR– of 0.3. von Heimburg *et al.* demonstrated an association between increasing TBSA and increasing PCT level (130). Neely *et al.* (131) did not identify any improvement using PCT to detect sepsis if compared with CRP. In a study by Su *et al.* (133) PCT and CRP were both increased in burn sepsis, but they were considered not to be reliable markers for the early diagnosis of this condition; Zu *et al.* made the same observation (134). Mokline *et al.* found that five days after burn injury, PCT serum concentration was significantly different ($P=0.001$) between infected and non-infected patients (5.44 ± 6.23 and 0.41 ± 0.64 ng/mL); a PCT cut-off value of 0.69 ng/mL showed the optimal sensitivity (89%), specificity (85%), LR+ (5.9), LR– (0.2) and DOR (45.8) (135). They concluded that PCT levels correlate closely with sepsis severity, could have a prognostic value in the outcome and repeated measurements were more useful than single values (135).

More recently a meta-analysis by Cabral *et al.* yielded an overall AUC of 0.87, a sensitivity of 77%, and a specificity of 65%. The mean PCT level was 46.8 ng/mL (95% CI, 2.5–91.1) in patients with sepsis and 0.9 ng/mL (95% CI, 0.1–1.6) in those without sepsis. These results led the authors to propose that PCT >1.5 ng/mL could be an indicator of sepsis and should, therefore, spur clinicians to commence antibiotic therapy (sensitivity 43%, specificity 83%, LR+ 2.5, LR– 0.4 and DOR 3.8) (136).

Results on the utility of PCT levels to early detect sepsis in burned patients are controversial, probably the use of different combinations of different biomarkers could overcome their individual limitations (137,138).

PCT in infectious complications of pancreatitis

Infection of pancreatic necrosis (IPN) represents an important complication in acute pancreatitis (AP) and the role of PCT in this condition remains controversial. Some studies, however, highlight its usefulness in anticipating the risk of developing IPN (139–142). In 2000, Rau *et al.* found that PCT concentrations were significantly higher in IPN than in patients with severe necrosis, whereas CRP levels did not differ in both groups. IPN could be predicted with a PCT concentration ≥ 1.8 ng/mL on at least two consecutive days, showing 95% sensitivity, 88% specificity, LR+ 7.9, LR– 0.1, number needed to diagnose (NND) 139. A CRP cut-off value of 300 mg/L showed 86% sensitivity, 75% specificity, LR+ 3.4, LR– 0.3 and NND 18.4 (142).

In 2009 a systematic review assessed the value of PCT in predicting the severity of AP and the development of IPN. The pooled sensitivity of PCT for development of severe AP was 72%, specificity 76%, with a LR+ of 5.1, a LR- of 0.2, a DOR of 15.8 and NND 1.7. In the prediction of development of IPN pooled sensitivity was 80% and specificity 90%, with 8.9 LR+, 0.1 LR-, 40.4 DOR and 1.4 NND. The authors concluded that PCT was valuable in predicting the severity of AP and the risk of developing pancreatic necrosis (140).

Chen *et al.* explored if CRP and PCT, collected within early 48 hours of hospitalization, were independently related to the development of IPN during necrotizing pancreatitis (141). The cut-off value of CRP was 257.50 mg/L with a sensitivity of 44.8% and specificity of 89.1%, LR+ 4.1, LR- 0.2, DOR 6.6 and NND 2.9. The cut-off value of PCT was 1.39 ng/mL with a sensitivity of 60.9% and specificity of 75.0%, LR+ 2.4, LR- 0.4, DOR 4.7 and NND 2.8 (141). They concluded that the maximum levels of PCT and CRP within 48 hours of admission were an independent factor for IPN. Furthermore, the combined diagnosis with CRP, PCT, hematocrit and blood urea nitrogen, could predict the occurrence of IPN secondary to NP within 48 hours after admission (141).

The 2019 World Society of Emergency Surgery (WISES) guidelines for the management of severe acute pancreatitis recognise serum PCT as valuable tool in predicting the risk of developing infected pancreatic necrosis. However, the grade and strength of recommendation was 1B on the basis that the quality of evidence remained moderate due to RCTs with important limitations (143). The IAP/APA (International Association of Pancreatology/American Pancreatic Association) evidence-based guidelines, include PCT among the single serum markers (e.g., CRP, hematocrit, blood urea nitrogen) to predict AP, specifying that none of these are clearly superior or inferior to persistent systemic inflammatory response (144).

Iida *et al.* recently reviewed literature and their experience concerning serum PCT as a predictor of infectious complications after pancreaticoduodenectomy (PD) (145). In a study including 77 patients undergoing PD, PCT was the most significant factor predicting infectious complications on post-operative day 3 (sensitivity 87%; specificity 88%) (145). Conversely, in a review including 6 studies examining the role of preoperative and postoperative PCT and CRP, all reports demonstrated the usefulness of PCT as a predictor of infectious complications

in postoperative patients, but did not identify any advantage compared to CRP (145). They further noticed that the current cost of PCT in Japan was about 10 times that of CRP leading to the conclusion that this biomarker is less cost-effective than CRP for predicting infectious complications after PD (145).

Recently Komolafe *et al.* compared the diagnostic accuracy of CRP, PCT and LDH, either alone or in combination, in the diagnosis of NP in people with AP and without organ failure. The authors concluded that none of the tests were sufficiently accurate to suggest that they could be useful in clinical practice. In particular PCT at 0.5 ng/mL showed 75% sensitivity, 57% specificity, LR+ 1.7, LR- 0.6, DOR 4 and NND 3.1 (146).

Conclusions

Notwithstanding the fact that there are several RCT and observational trials assessing the usefulness of PCT in early diagnosis of septic events in different clinical settings (critically ill patients, burned and polytrauma patients), uncertainty remains with regard to its use in starting and stopping clinical decisions for antibiotics. *Table 1* shows the weight of the evidence supporting the role of PCT in different clinical conditions.

Positive and negative likelihood ratios (LR+; LR-), express the capacity of a test to increase certainty about a positive/negative diagnosis; the diagnostic odds ratios (DOR) combines the strengths of sensitivity and specificity (168); the NND, indicates the number of tests to carry out in order to gain a positive response for the presence of a disease (169). Only 16 of the LR+ cited in the references are greater than 5 and only 4 greater than 10. A LR equal to 1.0 is not helpful because it means that the PCT value is the same in the same number of sick and healthy subjects for the pathology considered. The greater than 1.0 the LR+ is, the greater the increase of disease probability. LR+ between 2–5 produce small increases in post-test probability of disease, 5–10 moderate increases and over 10 large increases (170). As suggested by McGee *et al.* a LR of 2 increases the probability by 15%, 5 by 30%, and 10 by 45% (170,171). This means that with a pre-test probability of 30% and a LR+ of 2, when the test is positive, post-test probability is only 45% (30%+15%).

In conclusion, definitive answers remain elusive owing to the heterogeneity of results obtained in different clinical setting, both in terms of diagnostic accuracy of PCT and in terms of its usefulness in guiding the discontinuation of antibiotic therapy.

Table 1 Study design; sample size; manufacturers; principal diagnosis; cut-off; sensitivity; specificity; positive and negative likelihood ratio, diagnostic odds ratio; number need to diagnose of PCT in different clinical settings (details in text)

Study design	Sample size	Manufacturer	Analyzer	Diagnosis	Cut-off, ng/mL	Sens. %	Spec. %	LR+	LR-	DOR	NND	Ref.
Infectious complications of burns												
Meta-analysis	830	Roche, Brahms, Biomerieux	PCT-Q, Vidas, E411 Lumitest	Suspected sepsis	1.47	77	65	2.2	0.5	6.2	2.4	(147)
Retrospective	150 (102 septic; 48 not-septic)	Brahms	Kryptor	TBSA \geq 15%	0.5	71	62	1.9	0.5	4.0	3.0	(136)
					1.0	52	77	2.3	0.4	3.6	3.4	(136)
					1.5	43	83	2.5	0.4	3.7	3.8	(136)
Prospective	43	Brahms	Lumitest	Sepsis	1.50	88	92	11	0.1	84.3	1.3	(129)
				Respiratory infection	0.52	77	88	6.4	0.2	24.6	1.5	(129)
				Wound infection	0.56	76	80	3.8	0.3	12.7	1.8	(129)
Prospective	121 (44 septic; 77 not septic)	Brahms	Lumitest	Sepsis in burn	0.69	89	85	5.9	0.2	45.8	1.4	(135)
Retrospective	38	Brahms	Cobas	Sepsis in burn	10.3	44	90	4.4	0.2	7.1	2.9	(148)
					2.0	67	64	1.9	0.5	3.6	3.2	(148)
					2.4	75	70	2.5	0.4	7.0	2.2	(148)
Prospective	37 (26 septic; 11 not septic)	Brahms	Cobas	Suspected sepsis in burn patients	0.76	75.7	78.6	3.5	0.3	11.4	1.8	(149)
Prospective	175 (24 survivors: no infection; 93 survivors: infection; 58 non-survivors)	Brahms	Vidas	Sepsis in burn	1.7	77.6	82.1	4.3	0.2	15.9	1.7	(150)
Prospective	60 (30 septic; 30 not septic)	Brahms	PCT-Q	Sepsis in burn	0.5	100	89.3	9.3	0.1	1.1	1.1	(127)
Prospective	25	Brahms	Lumitest PCT-Q1	Sepsis in burn	0.534	42.4	88.8	3.8	0.3	5.8	3.2	(128)
Infectious complications of polytrauma												
Prospective	80 (23 neither; 24 SIRS; 33 sepsis)	Brahms	Kryptor	Sepsis in post-trauma	0.8	87	82	4.8	0.2	30.5	1.4	(98)
Prospective	275 (200 not septic; 75 septic)	Biomerieux	Vidas	Sepsis in post-trauma	2	91	66	2.7	0.4	19.6	1.8	(116)
Central nervous system infections												
Prospective	50 (20 bacterial meningitis; 20 viral meningitis; 10 controls)	Brahms	Lumitest	Bacterial meningitis	2.0	100	60	2.5	0.4	1.7	1.7	(55)
Prospective	48 bacterial meningitis	Brahms	Kryptor	Bacterial meningitis	0.28	97	100	0.0	0.0	1.0	1.0	(59)
Prospective	98 acute meningitis	Brahms	Elecsys	Bacterial meningitis	0.74	95	100	0.0	0.0	1.1	1.1	(67)
Retrospective	63 (20 bacterial meningitis; 43 non bacterial meningitis)	Brahms	Vidas	Bacterial meningitis	1	90	100	0.0	0.0	1.1	1.1	(66)
Prospective	50 (19 bacterial meningitis; 31 non bacterial meningitis)	Brahms	Vidas	Bacterial meningitis	0.5	100	87.09	7.7	0.1	1.1	1.1	(65)

Table 1 (continued)

Table 1 (continued)

Study design	Sample size	Manufacturer	Analyzer	Diagnosis	Cut-off, ng/mL	Sens. %	Spec. %	LR+	LR-	DOR	NND	Ref.
Prospective	50 (16 bacterial meningitis; 24 non bacterial meningitis; 10 controls)	RayBioHuman	ELISA Kit	Bacterial meningitis	1.2	68.8	83.3	4.1	0.2	11.0	1.9	(62)
Prospective	38 (18 bacterial meningitis; 20 non bacterial meningitis)	Brahms	Lumitest	Bacterial meningitis	0.5	95	94	15.8	0.1	297.7	1.1	(75)
Prospective	78 (14 bacterial meningitis; 64 non bacterial meningitis)	Brahms	Vidas	Bacterial meningitis	0.15	50	80	2.5	0.4	4.0	3.3	(76)
Prospective	70 (40 septic meningitis; 15 aseptic meningitis; 15 controls)	Raybiotech	ELISA	Bacterial meningitis	15	92	67	2.8	0.4	23.3	1.7	(77)
Prospective	45 (26 bacterial meningitis; 19 non bacterial meningitis)	NA	ELIZA M6	Bacterial meningitis	0.05	79	81	4.2	0.2	16.0	1.7	(80)
Prospective	120 (45 bacterial meningitis; 75 non bacterial meningitis)	Brahms	Lumitest	Bacterial meningitis	0.5	98	65	2.8	0.4	91.0	1.6	(82)
Prospective	50 (12 bacterial meningitis; 38 non bacterial meningitis)	NR	ELISA	Bacterial meningitis	0.6	66.7	59.3	1.6	0.6	2.9	3.8	(83)
Critically ill patient												
Prospective	551	Brahms	Elecsys	Sepsis	0.5	52	73	1.9	0.5	2.9	4.0	(7)
Retrospective	192 (64 candidaemia; 128 bacterial sepsis)	Brahms	Vidas	Candida spp. infection	2.5	78	72	2.8	0.4	9.1	2.0	(20)
Prospective	76 (33 SIRS with infection; 18 SIRS without infection; 25 controls)	Boditech Med Inc.	Ichroma PCT test	Sepsis	0.85	61	89	5.5	0.2	12.7	2.0	(151)
Prospective	219 (120 septic; 99 not septic)	Brahms	Kryptor	Sepsis	0.74	73	74	2.8	0.4	7.7	2.1	(152)
Prospective	207 (38 systemic bacterial infection; 77 localized bacterial infection; 22 suspected bacterial infection; 70 non infectious disease)	Brahms	Elecsys	Sepsis	0.5	86	79	4.1	0.2	23.1	1.5	(153)
Prospective	388 (246 septic; 142 controls)	Brahms	Lumitest	Sepsis	0.28	92	96	23.0	0.0	276.0	1.1	(154)
Prospective	144 (44 severe sepsis; 56 septic shock; 44 not septic)	ThermoFisher	Kryptor	Sepsis	0.5	80	59	2.0	0.5	5.8	2.6	(155)
Prospective	92	Brahms	Vidas	Sepsis	4.4	84	84	5.3	0.2	27.6	1.5	(156)
Prospective	145 (42 SIRS; 70 bacterial sepsis; 33 systemic candidiasis)	Brahms	Lumitest	Candida spp. infection	0.88	86	83	5.1	0.2	30.0	1.4	(157)
Prospective	100 (85 infected; 15 not infected)	Roche	PCT-Q	Septic shock	0.85	79	73	2.9	0.3	10.2	1.9	(158)
Prospective	301 (149 no infection; 91 infection without bloodstream involvement; 61 bloodstream infection)	Brahms	Lumitest	Sepsis	1.41	65	66	1.9	0.5	3.6	3.2	(159)

Table 1 (continued)

Table 1 (continued)

Study design	Sample size	Manufacturer	Analyzer	Diagnosis	Cut-off, ng/mL	Sens. %	Spec. %	LR+	LR-	DOR	NND	Ref.
Retrospective	270 (145 septic; 125 not septic)	Brahms	Lumitest	Sepsis	0.5	88	64	2.4	0.4	13.0	1.9	(160)
Prospective	300 (107 septic; 193 not septic)	NR	NR	Sepsis	0.44	83	54	1.8	0.6	5.7	2.7	(161)
Respiratory tract infections and COPD												
Prospective	78	NA	NA	COPD—acute bacterial exacerbation	0.76	79	93	11.3	0.1	50.0	1.4	(162)
Prospective	214 (164 cases; 50 controls)	NA	NA	COPD—acute bacterial exacerbation	NA	69	83	4.1	0.2	10.9	1.9	(163)
Retrospective	63	Brahms	Kryptor	COPD—acute bacterial exacerbation	0.25	63	67	1.9	0.5	3.5	3.3	(164)
Prospective	77	Biomerieux	miniVidas	COPD—acute bacterial exacerbation	0.4	61	67	1.8	0.5	3.2	3.6	(165)
Prospective	240	Brahms	Kryptor	COPD—acute bacterial exacerbation	0.25	31	96	7.8	0.1	10.8	3.7	(166)
Meta-analysis	NA	NA	NA	COPD—acute bacterial exacerbation	0.35	60	76	2.5	0.4	4.8	2.8	(37)
Prospective	35 (20 cases; 15 controls)	Shenzhen New Industry Biomedical Engineering Co	Lumino analyzer	COPD—acute bacterial exacerbation	0.15	75	80	3.8	0.3	12.0	1.8	(167)
Meta-analysis	2,408	NA	NA	Pneumonia	NA	55	76	2.3	0.4	3.9	3.2	(31)
Infectious complications of pancreatitis												
Prospective	61	Brahms	Lumitest	Infected necrosis in acute pancreatitis	1.8	95	88	7.9	0.1	139.3	1.2	(142)
Meta-analysis	976	Brahms	Lumitest	Severe acute pancreatitis	0.5	73	87	5.6	0.2	18.1	1.7	(140)
Prospective	215	NA	NA	Infected pancreatic necrosis	NA	80	91	8.9	0.1	40.4	1.4	(140)
Retrospective	77	NA	NA	Infected pancreatic necrosis	1.39	61	75	2.4	0.4	4.7	2.8	(141)
Systematic review	242	NA	NA	Post-pancreaticoduodenectomy infection	1.8	87	88	7.3	0.1	49.1	1.3	(145)
Systematic review	242	NA	NA	Pancreatic necrosis	0.5	75	57	1.7	0.6	4.0	3.1	(146)

Sens, sensitivity; Spec, specificity; LR+, positive Likelihood ratio; LR-, negative Likelihood ratio; DOR, diagnostic odds ratio; NND, number need to diagnose; TBSA, total body surface area; COPD, chronic obstructive pulmonary disease; NA, not available; SIRS, systemic inflammatory response syndrome; Ref., reference.

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