*Review*

# Diagnostic and prognostic roles of procalcitonin and other markers in pneumonia: A literature update

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**Abstract:** Community-acquired pneumonia (CAP) is among the most common causes of death and one of the leading healthcare concerns worldwide. It can evolve into sepsis and septic shock, which have a high mortality rate, especially in critical patients and comorbidities. The definitions of sepsis were revised in the last decade as "life-threatening organ dysfunction caused by a dysregulated host response to infection". Procalcitonin (PCT), C-reactive protein (CRP), and complete blood count including white blood cells are among the most commonly analyzed sepsis-specific biomarkers also used in pneumonia in a broad range of studies. It appears to be a reliable diagnostic tool to expedite care of these patients with severe infections in the acute setting. PCT was found superior to most other acute phase reactants and indicators, including CRP as a predictor of pneumonia, bacteremia, sepsis and poor outcome. In addition, PCT use is beneficial to judge timing for cessation of antibiotic treatment in most severe infectious states. The clinicians should be aware of strengts and weaknesses of known and potential biomarkers in expedient recognition and management of severe infections. This manuscript is intended to present an overview of the definitions, complications and outcomes of CAP and sepsis, with special regard to PCT and other important markers.

**Keywords:** pneumonia; bacteremia; sepsis; procalcitonin; diagnosis; biomarker; outcome; antibiotic stewardship

## 1. Introduction

*Community-acquired pneumonia (CAP): Definitions and diagnostic approaches*

Pneumonia is the acute infectious process of the pulmonary parenchymal tissue. Community-acquired pneumonia (CAP) is the leading healthcare concern worldwide. CAP inflicts patients in the community, as opposed to nosocomial pneumonia (1,2). Pneumonia is defined as symptoms and clinical manifestations such as fever, cough, dyspnea, new onset of fatigue and pleuritic chest pain are common symptoms (3).

The annual incidence of CAP in developed countries is about 1% (4), while around one-third of the patients need to be admitted to hospital (5). A population-based study in Germany showed that the yearly incidence of CAP admitted to hospital was 0.3% (6). Male patients are reported to be more likely to be admitted to hospital than females (7).

CAP is associated with significant morbidity, mortality, and healthcare expenses. Mortality in hospitalized patients with CAP is reported to range between 10% and 12% (8).

Although CAP has a predilection for the elderly, newborns or young infants, it is reported at all ages, especially those with compromised immunity and/or other comorbidities. Immune compromise and age-related changes make these subgroups more vulnerable to pneumonia. For example, the incidence of CAP in the elderly (>65 years of age) comprise around 3% inhabitants/year (9,10).

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## 2. Clinical findings

No clear group of symptoms and signs has been found to reliably predict whether or not the patient has the disease (11). Certain clinical findings support the diagnosis of pneumonia. Signs and symptoms of CAP include cough, fever, sputum production, chest pain (mostly pleuritic in nature), dyspnea, while crackles, and diminished or bronchial breath sounds, which may be encountered on physical examination. Mucopurulent sputum production is most frequently detected in conjunction with pneumonia of bacterial origin, whereas watery sputum is suggestive of atypical pathogens. Nausea, vomiting, diarrhea, and mental status changes are also noted frequently. Chest pain is a major complaint in a third of cases, chills in up to a half, and rigors in 15% (12). Acute onset of illness, pleuritic chest pain, and WBC count >15 x 109/L have been associated with S. pneumoniae aetiology (13).

## 3. The diagnosis of CAP

The diagnosis of CAP generally necessitates an infiltrate on CXR in a patient with fever, dyspnea, cough, and sputum.

While *Streptococcus pneumonia* is the most commonly isolated agent, *Staphylococcus aureus*, *Haemophilus influenzae*, *Enterobacteriaceae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumonia* are among the culprits in patients with CAP. A Swedish study disclosed that in hospitalized patients with CAP, Pneumococci are the dominant agent, followed by *Haemophilus influenzae*, and *Mycoplasma pneumonia* (14,15). On the other hand, elderly patients have a different order of frequency of culprit agents in CAP (Table 1) (10,16, 17)

**Table 1.** Frequency of etiologic agents of Community-acquired pneumonia (CAP) in elderly patients.

| | |
|---|---|
| Streptococcus pneumoniae | up to 50% |
| Atypical (Legionella pneumophila and others) | up to 25% |
| Haemophilus influenzae | 0–13% |
| Staphylococcus aureus | 0–7% |
| Methicillin-resistant Staphylococcus aureus (MRSA) | 0–6% |
| Gram-negative bacilli including Pseudomonas aeruginosa | up to 27% |
| Virus | 0–8% |
| Aspiration pneumonia | 10% |

**Table 2.** Differential diagnosis of patients with cough. These entities commonly masquerade CAP.

| |
|---|
| Pulmonary embolism |
| Cryptogenic organizing pneumonia |
| Tuberculosis, Actinomycosis |
| Pulmonary vasculitis, lupus pneumonitis and hypersensitivity pneumonitis, acute or chronic eosinophilic pneumonia |
| Sickle cell syndrome, sickling crisis |
| Acute hemorrhage in the alveoli |
| Radiation pneumonitis |
| Leukemia and neoplasms such as bronchogenic carcinoma |
| Drug-induced pulmonary infiltration |

### *3.1. Radiological findings*

#### 3.1.1. Chest X-rays

Chest X-rays (CXR, PA and lateral) can mostly be adequate for decision making in suspected patients, which render CT scans not necessary in selected situations. The

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diagnosis of CAP is generally based on the presence of predefined clinical properties and is supported by simple imaging modalities, mostly by CXR (18). In this regard, CAP presents as one of three patterns as follows:

a) focal nonsegmental or lobar pneumonia,
b) bronchopneumonia in multiple foci or lobular pneumonia,
c) patterns compatible with interstitial pneumonia (focal or diffuse)

False-negative CXR can be seen in the initial stage of pneumonia in some situations, including patients with neutropenia, dehydration, and immunocompromise. A special example is *Pneumocystis carinii* pneumonia (PCP, a.k.a. *Pneumocystis jirovecii* pneumonia) in which spiral CT scans can be needed to visualize findings suggestive of infection adequately.

High-resolution computed tomography (HRCT) usually demonstrate the pattern and distribution of pneumonia more accurately than the CXR (19,20).. It is not routinely ordered in the diagnosis of patients with suspected CAP because of cost-effectiveness principles. Instead, HRCT con be ordered as an adjunct to CXR in selected cases. For example, HRCT has been postulated to be a useful alternative to RT-PCR in the diagnosis of COVID pneumonia, in which a negative test can rule out the diagnosis of COVID pneumonia (21).

#### 3.1.2. Ultrasound

Lung USG is employed more commonly in the last decades to diagnose pneumonia with inappreciable diagnostic value in the patients *in extremis* who are hard to be transferred to the radiology unit. The sensitivity of lung USG was reported to be between 80% and 90% and the specificity between 70% and 90% (22,23).

### *3.2. Blood count*

Increased WBC count (up to 30,000 /mm$^3$) and a leftward shift are common findings, whereas leukopenia is suggestive of a poor outcome. Co-existence of fever, cough, tachycardia, and crackles have a sensitivity below 50% when CXR was used as a reference standard (24).

*Legionella* spp., Influenza A and B, MERS-CoV and SARS-CoV, and community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) are some of these organisms.

### *3.3. Blood cultures*

Blood cultures (BC) and sputum Gram stain and culture should be obtained and studied in severe, hospitalized patients. BC are expected to be positive in around one-fifth of patients. Especially patients with severe CAP requiring ICU admission should have BC, *Legionella* and pneumococcus urinary antigen tests, and sputum culture.

BC are recommended in severe and critical patients with CAP because positive results indicate the specific microbial diagnosis in most cases (25). False-positive BC can be encountered in one-tenth of the patients (26). Studies pointed out that positive BC rarely results in a change of antibiotic treatment regimens (27).

### *3.4. Molecular methods*

Potential advantages of molecular methods are speed and enhanced sensitivity and specificity (28,29). These methods are available in most centers to elucidate viral agents and some bacteriae including *M. pneumoniae* and *Legionella pneumophila.*

### *3.5. Polymerase chain reaction*

Polymerase chain reaction (PCR) boosts the accuracy of the microbiological tests for patients with CAP with its rapid turnaround time (30-32). Since PCR specimens can be

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contaminated by the airway flora, a quantitative or semiquantitative PCR assay is needed in most cases (30,33,34).

### *3.6. Lactate*

Lactate is another biomarker with diagnostic and prognostic value in most severe infections (35). Research disclosed that lactate was able to predict poor outcomes in CAP patients in the acute setting and augmented the predictive power for death (36). High lactate value is associated with mortality of up to one-thirds of the samples in patients with CAP. An elevated lactate level suggests hypoperfusion and a marker for grave clinical course (37,38). In accord with the updated criteria for sepsis, both hypotension requiring inotropic support and serum lactate level above 2 mmol/L are necessary for the recognition of septic shock (39).

A recent study analyzed the effectiveness of adding lactate levels to the Rapid Emergency Medicine Score (REMS) scoring system to predict mortality and outcomes in patients over 40 years of age who present to the ED with dyspnea (40). The REMS+L score ($p$<0.001) was superior to the REMS ($p$<0.001) and lactate values ($p$ < 0.001) in predicting mortality.

### *3.7. mHLA-DR*

Zhuang et al. evaluated the expression of monocyte human leukocyte antigen-DR (mHLA-DR) measured within 24 hours after admission to predict 28-day survival, and mHLA-DR levels were found to be higher in patients with mortality when compared to survivors (41).

### *3.8. C-reactive protein (CRP)*

As another marker of inflammation, C-reactive protein (CRP) has a limited role in diagnosis of pneumonia. A CRP level above 40 mg/L have a sensitivity of 70% to 73% and a specificity of 90% to 65% in diagnosing bacterial pneumonia (42,43). Another study by Boussekey et al. cited that CRP had lower sensitivity when compared to PCT for the recognition of bacterial respiratory infection (44).

Use of CRP has only been shown to be informative in ruling out pneumonia initially in the outpatient setting. In this group, evaluation of signs and symptoms identified diagnostic risk accurately in around one-fourth of patients (45). On the other hand, the majority of patients in whom diagnostic doubt remained, CRP levels were useful to exclude pneumonia.

The predictive power of CAP was improved by adding biomarkers such as CRP to the other well-known scores. Menendez et al. reported that the added value of CRP to PSI, CURB-65 or CRB-65 augmented the prediction of death for hospitalized patients (46). These combinations retained a sensitivity of 0.77 and a specificity of 0.78, and therefore, it can be valued as a prognostic instrument, hampered by a lack of sensitivity and/or specificity in individual decision making.

### *3.9. p-calprotectin*

p-calprotectin has been recently reported to be an useful aid in sepsis-suspected patients. This biomarker has been found to be significantly elevated in critical patients after assessment by a multidisciplinary team (47). P-calprotectin was superior to traditional biomarkers in predicting the need for intensive care.

### *3.10. Procalcitonin (PCT)*

PCT, on the other hand, is a 116-amino acid precursor polypeptide for calcitonin produced in C cells of the thyroid that is released in response to microbial toxins and proinflammatory mediators such as IL-1B (interleukin-1beta, TNF-$\alpha$, and IL-6, bacterial products (eg, lipopolysaccharides) and necrotic tissue cells, immune-reactive calcitonin (48). It

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acts a factor to reduce serum calcium levels and is detectable in the blood of healthy adults that rapidly rises 1000-fold with severe critical illness (49). PCT also responds to modulate immunity-related functions, vasomotility and microcirculation, and changes in cytokines expression during hypoperfusion states mediated by endotoxins (50,51). PCT is produced and converted to calcitonin within the C-cells in the thyroid glands of healthy people without an inflammation, presenting very low PCT levels (< 0.1 ng/mL) (52).

PCT is a widely used serum biomarker which is closely related to bacterial structure and severity of the infection. It is most specific to infections incited by bacteria as it is attenuated by INF9 expressed in response to viral infections (53,54). The metabolic response to elevated PCT in critical illness is not known. The inflammatory response is critical to understand metabolic changes during extreme stress (**55)**.

PCT is accepted as a valuable inflammatory biomarker to discern bacterial from viral and other causes of pneumonia (28,56). Besides acute bacterial infections, PCT help identify various medical conditions including post-surgical anastomotic leaks, acute kidney injury, and consequences of intracerebral hemorrhage (57). Research revealed that PCT levels rise in correlation with bacteremia and severe infection and predicts death in patients with CAP and sepsis (58,59). Studies from Northern Europe pointed out a link between elevated PCT readings and pneumonia severity (60,61).

PCT is not routinely worked up in the diagnostic process of CAP as its predictive accuracy is only moderate. Most clinicians order a PCT level at the time of diagnosis, and serially to help decide the most beneficial duration of antibiotics.

3.10.1. Comparisons of PCT with CRP and other markers

Some investigations highlighted its diagnostic value in different clinical scenarios. PCT was superior to CRP as a diagnostic indicator for predicting bacteremias, for discriminating bacterial from nonbacterial infections, and for determining bacterial species (62). Area under the ROC curve of PCT and CRP were 0.79 and 0.66, respectively. The optimal cutoff values were 0.5 mcg/L with a sensitivity of 70% and specificity of 70% for PCT and 50.0 mg/L with a sensitivity of 63% and specificity of 65% for CRP. When the optimal cutoff value was used as a reference, the OR was 71.11 and the hazard ratio was 6.27 for PCT >2.0 mcg/L, and the risk of BC positivity was markedly elevated.

Some studies advocated CRP against PCT in specific subgroups. For example, CRP was better than PCT at predicting pneumonia as demonstrated in a retrospective study of elderly patients with comorbid diseases (63).

Zhang et al. compared patients with sepsis and those with local inflammatory diseases admitted to the ICU in China (64). The combined AUC was greater than the sum of IL-10, IL-17, and PCT ($P < 0.05$). A clinical decision curve analysis disclosed that the three combined tests outperformed the individual tests in terms of total clinical benefit rate. It was concluded that there was a considerable net therapeutic benefit ranging from 3% to 87%.

The analyses of soluble interleukin-2 receptor (sIL-2R), tumor necrosis factor-a (TNF-a), and PCT has a considerable benefit in the recognition of septic course in closed abdominal injury complicated with severe multiple injuries (65). The high concentrations of PCT and TNF-a can be used as valuable predictors of sepsis.

3.10.2. PCT in COPD

An elevated PCT level (HR: 1.02, 95% CI: 1.00–1.03) is among the variables predicting death, namely, the age (hazard ratio: 1.12, 95% CI: 1.05–1.19), a history of cancer (HR: 7.04, 95% CI: 2.22–22.36) (66).

The use of PCT-based protocols in COPD exacerbations reduced the use of antibiotics (RR: 0.56, 95% CI: 0.43–0.73) and decreased the number of days of antibiotic administration (difference in days: −3.83, 95% CI: −4.32–0.35) but had no effect on the total length of hospital stay and mortality (67).

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In a study by Corti *et al*., patients with COPD exacerbations followed up for 28 days were randomized to PCT and control groups, and the rate of antibiotic use was more than 41% in the PCT group, whereas it was 67% in the controls (68). Similarly, Stolz *et al*., reported that PCT-mediated care reduced prescriptions of antibiotics (40% vs. 72%) (69).

PCT worked up in conjunction with CRP was advocated as a more useful test in the recognition and management of acute exacerbations of COPD (70). The levels of PCT and CRP were (1.97±0.13) μg/L and (7.34±2.66) mg/L respectively in the infection group after treatment, which was significantly much lower than the levels before treatment. Levels of CRP in combination with PCT is a reliable index for detection of bacterial infection in these patients.

According to the results of a retrospective cohort study conducted by Ulrich *et al*. in 2019, in which records of 238 COPD exacerbation cases were evaluated, the duration of antibiotic administration was not shortened in patients directed by PCT within a 6-month period, and no difference was noted in regard to mortality (71). Meanwhile, it was reported that the rate of 30-day readmissions was reduced in the group, in which PCT was measured compared to the group in which it was not worked up (21% vs. 36%).

In brief, use of biomarkers will not be sufficient alone for prognostic purposes in the management of COPD exacerbations. It may be considered to use PCT and CRP levels together with other signs and symptoms to identify the etiology of exacerbation and to predict the probability of re-admission to the hospital (72). The use of PCT-guided antibiotics in patients admitted to the hospital with COPD exacerbation does not alleviate mortality compared to standard care, and thus, routine PCT level measurement is not necessary.

#### 3.10.3. Sepsis and PCT

Fever associated with signs of shock is commonly caused by sepsis which encompasses a wide spectrum of illness caused by infection and its complications. The incidence of sepsis is increasing worldwide with a high death toll. The mortality rate of severe sepsis is around 30–50%, and Septic shock has a mortality rate of more than 50% (73). Expedient recognition and management definitely decreases mortality. On the other hand, the symptomatology and findings of a patient with sepsis are similar to other inflammatory reactions, especially when the source of infection cannot be identified.

Appropriate management comprises empirical antibiotics and resuscitation. A PCT level > 2 SD above normal is a typical finding of sepsis laboratory work up (74).

#### 3.10.4. Should we use PCT alone or PCT-based scores?

Tsui et al. proposed a PCT-based score which has been revealed to perform better in detecting sepsis and compared this with serum PCT levels alone, C-reactive protein, and infection probability score (75). The PCT-based score performed well in detecting sepsis (AUROC 0.80; 95% confidence interval (CI) 0.74–0.85; sensitivity 0.70; specificity 0.76), which was better than the other competitors.

#### 3.10.5. Value of PCT in Elderly Patients

PCT was proven useful in elderly patients suspected to have bacteremia. Lee et al. reported that PCT was not inferior to other tests in recognition of bacterial infection (76). On the other hand, the deficient accuracy of the test withheld recommendations on the use of the test in isolation. In a recent study on the elderly patients with sepsis, PCT, IL-10, IL-6, and IL-5 were found accurate in estimating ICU follow-up, but were not effective in predicting mortality (77).

#### 3.10.6. Use of PCT in Congestive heart failure (CHF)

Elderly patients with CHF commonly present at the ED with respiratory symptoms (8). Some of the cases can have pneumonia complicating CHF and/or signs and symptoms

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of CAP can be confused with those of CHF. The use of biomarkers such as PCT measurement will help identify patients with bacterial infection and guide antibiotic therapy. Elderly patients with CHF and elevated PCT levels indicate high probability of bacterial infection (78,79).

3.10.7. Pneumonia and CAP is also an important acquired morbidity in patients residing in nursing homes.

PCT levels were recorded to be 4.7 +- 5 ng/mL in non-survivors and 0.86 +- 1 ng/mL in survivors in this group of patients ($P < .001$) (80). The AUC for PCT in estimating mortality was 0.84 (95% CI 0.70–0.98, $P = 0.001$). A PCT level measured as > 1.1 ng/mL on presentation was cited as an independent predictor of mortality.

3.10.8. Use of PCT in chronic renal insufficiency (CRI)

PCT levels are higher in patients with reduced renal function, and levels can be lowered after dialysis by around 20–80% (81-84). In general, PCT and CRP show poor sensitivity but acceptable specificity in diagnosing bacterial infection among patients with CRI. Their negative likelihood ratio is low, which render their value as a rule-out test questionable.

In a meta-analysis published by Lu et al, the positive LR for PCT (LR)+ 6.02, 95% CI 3.16–11.47) was sufficiently high as a rule-in diagnostic tool, while the LR- was not low enough for a rule-out test (LR− 0.31, 95% CI 0.17–0.57) (85). Therefore, clinicians are not recommended to rule out bacterial pneumonia or sepsis in a patient with normal levels of PCT.

Mean levels of serum PCT in ESRD patients on dialysis to be 0.7” ng/mL, and more than a half (57%) of dialysis patients had pre-dialytic levels above 0.5 ng/mL (86). Lee et al. measured serum PCT levels in ESRD patients on antibiotic therapy for bacterial infection (ESRD infection [iESRD] group), and compared with those of ESRD patients on dialysis without any infection signs (ESRD control [cESRD] group (87). Serum PCT is found a strong indicator of infection in ESRD patients, using 0.75 ng/mL as a cutoff value. 70% of uninfected children were demonstrated to have pre-dialytic PCT levels >0.5 ng/mL and were reduced substantially by 40% via dialysis (88).

3.10.9. PCT in obesity

Being overweight frequently accompanies insulin resistance. PCT is reported to be an important marker of fat accumulation and metabolic parameters associated with obesity. Boursier et al. have demonstrated that PCT can be a valuable marker of fat accumulation and metabolic parameters in obese individuals (89). PCT is postulated to be useful to schedule exercise, weight loss (57).

3.10.10. Use of PCT in children

Damman et al. sought for the diagnostic accuracy of PCT in predicting bacteremia in febrile children with indwelling central lines (90). They reported that a PCT level of >=0.6 ng/mL was the best cutoff point with a sensitivity of 85.6% and a specificity of 66% (AUC 0.85) which approved PCT as a sensitive biomarker predicting bacteremia in febrile children with a central line. Higher PCT was found to predict more severe pneumonia and longer hospital stay, in a study which enrolled around 490 children with pneumonia (91). The marker can be used to aid clinicians in evaluation of pneumonia severity accurately.

Although PCT is more accurate to predict severe infectious states when compared to CRP and other markers, it does not appear to be sensitive or specific enough to act as a reliable test for the recognition of sepsis (92). An elevated PCT level on admission indicates a poorer outcome for patients with sepsis or septic shock, albeit serial measurements provide more reliable estimation of the clinical course.

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3.10.11. H1N1 infection (Influenza) and PCT

Most patients are diagnosed on clinical grounds alone amidst influenza epidemics. ICU patients complicated by bacterial pneumonia had higher PCT levels than those having only H1N1 infection (6 mcg/L vs. 0.6 mcg/L) (93). The test had 80% sensitivity and 73% NPV in estimating pneumonia with the cut-off level accepted as 0.5 mcg/L. Bedside tests had a sensitivity around 50%, but specificity is above 95% (94,95).

3.10.12. Secondary bacterial infections

Wu et al. published a systematic review and meta-analysis, and pointed out that the LR+ for PCT was 2.31 (95% CI: 1.9–2.8) which is not adequate for its reliability as a diagnostic tool, while its LR- was low enough to employ as a rule-out tool (LR- = 0.26; 95% CI: 0.17–0.40) (96).

PCT has a high sensitivity, particularly for ICU patients, but a low specificity to diagnose secondary bacterial infections among patients with influenza. It can be a valuable rule-out test because of its high LR-, but cannot be used as a standalone rule-in test because of suboptimal LR+.

Rodríguez et al. demonstrated that PCT has a high negative predictive value (94%) and lower PCT readings appear to be a useful instrument to rule out coinfection, particularly for those without signs of hypoperfusion, in a prospective multicentric investigation (97). Of note, PCT (2.4 ng/mL vs. 0.5 ng/mL, $p<0.001$), but not CRP (25 mg/dL vs. 38 mg/dL; $p=0.6$) was higher in patients with coinfection.

3.10.13. Use of PCT to diagnose bacterial infection in patients with autoimmune diseases

Pooled specificity was calculated to be 0.90 (95% CI 0.85–0.93) for PCT and 0.56 (95% CI 0.25–0.83) for CRP to identify bacterial infections in a meta-analysis (98). The LR+ for PCT (7.3 [95% CI 5.1–10.4]) was adequate to make PCT a reliable diagnostic instrument, while the LR- (0.3 [95% CI 0.2–0.4]) was not adequately low to accept PCT as a reliable exclusion tool. In brief, PCT has higher diagnostic reliability when compared to CRP in the diagnosis of bacterial sepsis in patients with autoimmune disease, and PCT is more specific than sensitive. A PCT test is not suggested to be used in isolation as a rule-out test.

3.10.14. Principles of treatment

Empiric antibiotic therapy with a β-lactam combined with a macrolide, respiratory fluoroquinolones, or tetracyclines comprise a management approach commonly recommended for patients hospitalized with CAP. Prevalence of resistant microorganisms increased in the recent decades including *S. pneumoniae* that is resistant to frequently used antibiotics, (e.g., β-lactams, macrolides, and tetracyclines) (99).

3.10.15. Use of PCT in antibiotic stewardship

PCT is commonly recommended to be used to exclude CAP and thus identify patients who do not need antibacterial therapy. In a randomized controlled trial, use of a "PCT algorithm" helped shorten duration of antimicrobial therapy and lowered antibiotic-related adverse effect rates (100).

Stop Antibiotics on Procalcitonin guidance Study (SAPS) trial enrolled more than 1500 patients in the ICU with suspected or known infection (65% had a respiratory infection) (101). Clinicians stopped antibiotics when PCT levels were below 0.5 ng/mL or decreased by ≥80% from peak. The PCT-guided group had substantially less antibiotic use (7.5 vs. 9.3 defined daily doses) and lower 28-day mortality (19% vs. 25%) than controls. Identical thresholds of ≤0.5 ng/mL or ≥80 percent reduction from peak on day 5 were used in the Procalcitonin-Guided Antimicrobial Therapy to Reduce Long-Term Sequelae of Infections (PROGRESS) trial. Compared with usual care, PCT-guided antibiotic discontinuation had lower antibiotic use (5 vs. 10 days) and 28-day mortality (102). These suggestions are in line with the 2021 Surviving Sepsis Campaign and the 2016 IDSA antimicrobial

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stewardship guidelines for using PCT levels to guide antibiotic cessation in patients with suspected infections in the ICU (103,104).

Consensus algorithms differ with regard to timing of treatment (i.e. initiation in low-risk patients or discontinuation in high-risk patients) and PCT cut-off points for the recommendation/strong recommendation to discontinue antibiotics (≤ 0.25/≤ 0.1 μg/L in ED and inpatients, ≤ 0.5/≤ 0.25 μg/L in ICU patients, and reduction by ≥ 80% from peak levels in sepsis patients) (105). PCT levels > 0.25 μg/L necessitate initiation of antibiotics in those with CAP. In patients receiving antibiotics, PCT levels should be checked in around two to three days. Antibiotic discontinuation is considered in patients with a visible improvement and if PCT levels are either below 0.25 μg/L or have reduced > 80% from peak levels. Causes of treatment failure include empyema, multi-resistant strains, or incomplete antibiotic therapy, which should be searched in those without sufficient decrease in PCT levels.

Tonkin-Crine et al. performed a systematic review of seven studies on the results of interventions intended to influence physicians' antibiotic prescribing behaviour for pneumonia in ambulatory care (106). They found that PCT-guided management appears to reduce antibiotic prescribing in EDs (adjusted OR 0.3, 95% CI 0.3 to 0.4). The overall effect of these interventions was small but likely to be clinically important. Shared decision making seems to produce little or no difference to reconsultation for the same illness (RR 0.8, 95% CI 0.7 to 1) as compared to usual care.

#### 3.10.16. PCT-guided treatment

In brief, PCT-guided treatment of pneumonia and other respiratory infections helps reduce antibiotic consumption and improve clinical outcomes, although launched algorithms had differences in PCT cut-off points. If initial PCT levels are above 0.25 μg/L, a bacterial infection is unlikely and other illnesses (e.g. pulmonary embolism or heart failure) should be ruled out.

#### 3.10.17. Patients with respiratory infections other than CAP

Ventilator-associated pneumonia, acute bronchitis, and acute exacerbations of COPD and other chronic lung diseases, do not routinely require PCT levels for management. PCT work up can be reserved for selected cases in these situations.

#### 3.10.18. Value of PCT in outpatient follow-up

PCT can be ordered in combination with a positivity for influenza or COVID-19, to withhold antibiotics or stop them early, provided that there are no other signs of bacterial infection (eg, dense consolidation on chest imaging, increased WBC count, or positive BC) and that patient has close follow-up. Other experts prefer to treat empirically with antibiotics because bacterial CAP is hard to exclude definitively, the morbidity association with CAP is high, and outpatient treatment courses for CAP are short (eg, five days).

While data directly supporting PCT-guided antibiotic decision-making in outpatients with CAP are limited, one randomized trial comparing >150 outpatients with CAP found that clinical outcomes were similar and antibiotic exposure was decreased when PCT was used (107). A recent study evaluated 469 general practice patients with any kind of respiratory infections (108). Antibiotic use was reduced at a rate of 26% when PCT was used to guide antibiotic decision-making, while clinical outcomes were similar. Interestingly, point-of-care lung USG did not further reduce antibiotic prescription, although a potential added value cannot be excluded,

#### 3.10.19. Conditions which cause false positive and negative PCT levels

Table 3 summarizes and lists the conditions triggering increases in PCT levels with and without pneumonia. False positive and negative PCT elevations should be accounted for in clinical grounds before affecting decision making processes (109).

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**Table 3.** Procalcitonin (PCT) levels with regard to various microbiologic agents and clinical variables.

| | PCT >0.25 ng/mL | PCT <0.25 ng/mL |
|---|---|---|
| Bacterial **infections (PCT levels may not increase in case of ab**scesses or empyema) | | |
| Typical pneumonia agents | Most reported thus far | |
| Atypical pneumonia agents | *Legionella* spp, mycobacteria spp | *Chlamydia pneumonia, Mycoplasma pneumonia,* mycobacteria spp |
| **Viral agents** | None | All |
| **Fungal agents** | *Candida* spp | Mucormycosis, aspergillosis, coccidioidomycosis |
| **Parasitic agent** | *Plasmodium* spp (malaria) | |
| **Physiologic stress** | Trauma, surgery, burn, pancreatitis<br>Bowel ischemia<br>Cerebrovascular accident, intracerebral hemorrhage<br>Shock (all causes) | |
| **Toxin-mediated entities** | *Clostridioides difficile*-associated disease, mushroom poisoning | *C. difficile* colonization |
| **Comorbid diseases, immune and rheumatologic entities** | Kawasaki disease, renal and hepatic failure | Rheumatoid arthritis, gout and pseudogout, Behçet disease<br>Crohn's disease<br>Systemic lupus erythematosus, polyarteritis nodosa, temporal arteritis, granulomatosis with polyangiitis |
| **Malignant tumors** | Thyroid and lung cancers | Lymphoma and sarcoma<br>Splanchnic cancers (e.g., pancreatic and renal cell carcinoma) |

3.10.20. Blank areas for PCT use

Certain deficiencies limit use of PCT in critical decision making. These include severe inflammatory states such as major surgery, trauma, burn injuries, inhalational injury, pancreatic necrosis, and therapeutic hypothermia (110-112).

## 4. Conclusions

Pneumonia and sepsis are diseases of utmost importance to diagnose and treat emergently, since they convey a high death toll worldwide. Although an elaborate history and clinical examination are mainstays for an accurate diagnostic process, certain laboratory adjuncts can comprise invaluable aids in appropriate management. PCT is one of the most commonly analyzed sepsis-specific biomarkers also used in pneumonia in a broad range of studies, together with CRP, and complete blood count. It appears to be a reliable diagnostic tool to expedite care of these patients with severe infections in the acute setting.

PCT is an inflammatory biologic marker that can be beneficial in distinguishing between bacterial and nonbacterial causes of pneumonia. It was found superior to most other acute phase reactants and indicators, including CRP as a predictor of pneumonia, bacteremia, sepsis and poor outcome. In addition, PCT use is beneficial to judge timing for cessation of antibiotic treatment in most severe infectious states. The clinicians should

gauge pluses and minuses of the useful biomarkers in expedient recognition and management of severe infections.

PCT can guide antibiotic decisions for the treatment of acute respiratory infections to minimize antibiotic prescription and orders to improve outcomes in this regard. PCT algorithms may be adapted to the type of infection and the unique case scenario. PCT has shown potential benefits in antibiotic stewardship protocols.

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