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Procalcitonin in Antimicrobial Stewardship: Clinical Utility Across Infections and Healthcare Settings

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Abstract **Review Article**

Antimicrobial resistance (AMR) is a mounting global health threat, largely driven by the overuse and misuse of antibiotics. Procalcitonin (PCT), a biomarker that rises in bacterial infections, has gained attention as a tool for optimizing antibiotic use within antimicrobial stewardship programs (ASPs). This review explores the clinical utility of PCT in guiding antimicrobial decisions across diverse infections and healthcare settings, including intensive care units (ICUs), emergency departments, outpatient clinics, and special patient populations. PCT has demonstrated value in differentiating bacterial from non-bacterial infections, guiding the initiation and discontinuation of antibiotics, and reducing unnecessary antibiotic exposure. In ICU settings, randomized trials such as PRORATA and SAPS have shown that PCT-guided protocols can safely reduce antibiotic duration without compromising patient outcomes. In emergency and outpatient care, PCT supports decision-making in respiratory tract infections and exacerbations of chronic conditions, improving prescribing practices. In immunocompromised, pediatric, and renal patients, PCT shows promise but requires cautious interpretation. Integration of PCT into ASPs has shown positive impacts but faces barriers including cost, clinician confidence, and variability in implementation. PCT is a valuable adjunct to clinical judgment in antimicrobial stewardship, enabling targeted and judicious antibiotic use. Broader adoption of PCT-guided approaches, informed by clinical context and supported by stewardship infrastructure, may help curb AMR and enhance patient care.

Keywords: Procalcitonin (PCT); Antimicrobial resistance (AMR); Antimicrobial stewardship programs; Biomarker; C-reactive protein (CRP).

1. INTRODUCTION

1.1 Brief overview of antimicrobial resistance (AMR) and overuse of antibiotics

Antimicrobial resistance (AMR) is one of the top ten public health threats facing mankind globally. It is estimated that 4·95 million deaths associated with bacterial AMR and 1·27 million deaths attributable to bacterial AMR occurred in 2019.[1] AMR arises through a combination of biological mechanisms and human-driven factors. Spontaneous mutation, genetic transfer, and selective pressure are important biological mechanisms for the emergence and spreading AMR. Human-driven factors include: Overprescription, self-medication, and widespread use of antibiotics in animal feed and crops. Additionally, the lack of accurate and rapid diagnostics leads to inappropriate broad-spectrum antibiotic use.[2] AMR contributes to longer hospital stays, higher healthcare costs, and worse outcomes, particularly in septic patients.[3] Delay in early diagnosis and prompt management is associated with septic shock, organ failure, and death.[4,5] It is a most frequent cause of infection, particularly in lower-middle income countries (LMICs). An estimated 49 million sepsis cases and 11 million sepsis-associated deaths were reported worldwide in 2017 and accounting for every one in five deaths reported globally (WHO). Bacterial infections have remained an important cause of sepsis and sepsis-related mortality in all age groups worldwide.[6]

Currently, the culture-based procedures (automated or conventional) are gold standard for sepsis diagnosis, but are time-consuming and require at least 48 to 72 hours for final identification of pathogens and antibiotic susceptibility patterns. The culture susceptibility profile further helps clinicians to modify the empirical treatment.[7,8] Molecular-based diagnostic methods can shorten the turnaround time; however, these methods require considerable skill, initial investments,

and high recurring costs. Thus, these techniques are inappropriate for countries with limited resources or emergency laboratories.[9,10]

1.2 Importance of biomarkers in stewardship

Based on signs and symptoms, the clinical sepsis diagnosis is supported by biomarkers, which may have a role in guiding optimal antibiotic therapy. Several biomarkers can aid the physician in distinguishing between infectious and non-infectious origins of sepsis, including acute phase markers, cytokine markers, cell surface markers, etc. These kinetics also play a vital role in monitoring the severity of illness, and treatment may be escalated or de-escalated based on the findings of biomarkers.[11] However, the role of sepsis biomarker remains to be established, as their levels are also elevated during inflammatory states associated with non-infectious aetiologies, e.g., autoimmune and rheumatic disorders, myocardial infarctions, malignant tumours or post-surgery, birth stress in new-borns, acute graft-versus-host disease and different types of immunotherapies.[12,13]

1.3 Introduction to PCT: rationale for clinical use

Procalcitonin (PCT) is one of the important biomarkers that plays a crucial role in the diagnosis and clinical management of bacterial infections. PCT, a protein that consists of 116 amino acids, is a precursor to the hormone calcitonin and is produced by the thyroid C cells. Its clinical utility includes differentiation of bacterial and viral infections, as its kinetic levels rise in bacterial infections and remain low in viral infections and non-infectious inflammatory conditions. PCT is used as a severity and prognostic indicator and treatment may be modified or monitored based on the levels of PCT.[14,15] The study aims to review the evidence of PCT in guiding antimicrobial use across different clinical settings.

2. BIOLOGICAL BASIS AND INTERPRETATION OF PCT

2.1 Pathophysiology: PCT rise in bacterial vs. viral/non-infectious conditions

Generally, PCT is cleaved to produce calcitonin and is involved in calcium homeostasis. In healthy individuals, serum PCT levels are typically undetectable (<0.05 ng/mL). However, during systemic infections, PCT is produced in large quantities by various tissues and organs outside the thyroid, including the liver, lungs, kidneys etc.[16] The host's immune response is the key biological basis for this shift. In bacterial infections, the PCT production is stimulated by microbial toxins such as lipopolysaccharides (LPS) and pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Conversely, in viral infections, interferon-gamma (IFN-γ) suppresses PCT synthesis, making it a relatively specific biomarker for bacterial infections.[17]

2.2 Thresholds for decision-making

The PCT is present in healthy humans' blood in concentration of <0.05 ng/ml. It is released into the blood and levels begin to rise within 4–6 hours after the onset of a bacterial infection, peaking at around 12–24 hours, with a 24-hour half-life.[18] The PCT kinetics levels between 0.05 and 0.5 ng/mL are considered low and may suggest a localized infection or a non-infectious inflammatory process. Levels above 0.5 ng/mL indicate a higher probability of systemic bacterial infection or sepsis, with values exceeding 2 ng/mL strongly suggestive of severe sepsis or septic shock.[19] PCT cut-offs <0.5 µg/L or an 80–90% decrease from peak levels indicate recovery, allowing for potential antibiotic treatment discontinuation.[20]

2.3 Pros and cons compared to other markers (e.g., CRP, WBC)

Procalcitonin (PCT) offers several advantages over other inflammatory markers like C-reactive protein (CRP) and white blood cell (WBC) count, particularly in distinguishing bacterial infections and assessing their severity. PCT levels rise rapidly in response to bacterial infections, making it a more specific indicator for early detection and monitoring of bacterial infections compared to other inflammatory markers.[21] CRP is a non-specific inflammation marker; thus, the elevated CRP levels can be caused by various inflammatory conditions, not just bacterial infections. CRP levels may not rise as rapidly as PCT levels (secretion starts 4–6 h after stimulation and peaks at 36-48h) and can be used to monitor disease activity.[22] WBC counts can be elevated in response to various conditions, including viral infections and autoimmune diseases, making it less specific for bacterial infections.[23] The Comparative Heatmap of PCT vs CRP vs WBC diagnostic markers is depicted in **Figure 1.**

This heatmap illustrates a normalized comparison of three biomarkers—Procalcitonin (PCT), C-Reactive Protein (CRP), and White Blood Cell (WBC) count—across four criteria: specificity, response time (inverted for consistency), cost (inverted), and availability. The overall score represents the sum of the normalized values across these criteria to provide an intuitive comparative assessment. (Azzini *et al.,* (2020) [21], Hu *et al.,* (2017) [22], Magrini *et al.,* (2014) [23]).

PCT levels correlated with bacterial infections severity, providing valuable information for the appropriate use of antibiotics and monitoring patient progress.[24] While CRP levels can be used to monitor the effectiveness of treatment for inflammatory conditions, however may not accurately reflect the severity of the infection.[22] Furthermore, PCT testing may not be as readily available in all hospital settings as routinely used as CRP or WBC count. PCT testing can be more expensive than CRP or WBC testing, potentially limiting its widespread use.[25] CRP testing and WBC

count are generally inexpensive and widely available in most hospitals and clinics.[26,27]

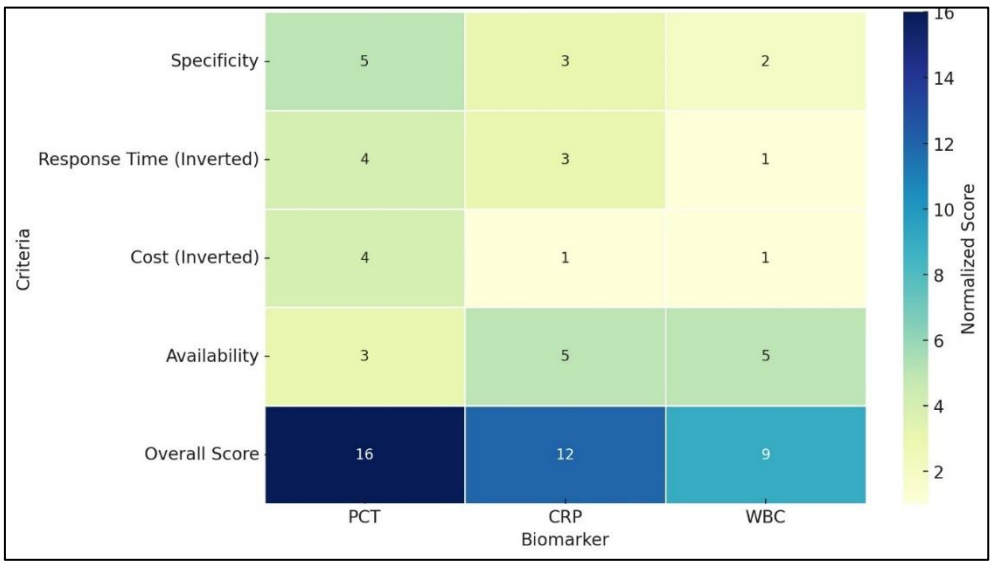

Figure 1: Normalized Comparative Heatmap of Diagnostic Markers: PCT vs CRP vs WBC.

3. PCT IN ANTIMICROBIAL STEWARDSHIP: KEY CLINICAL SETTINGS

3.1 Intensive Care Unit and Hospitalized Patients

Procalcitonin has emerged as a valuable biomarker for antimicrobial stewardship in intensive care unit (ICU) and inpatient settings, where distinguishing bacterial infections from non-infectious causes of systemic inflammation is critical yet often challenging. PCT levels rise rapidly (within 6–12 hours) in response to bacterial infections and decline with effective treatment, making it a dynamic marker for guiding antibiotic decisions in acutely ill patients.[15] One of the most compelling use cases for PCT in ICUs is in patients with sepsis or suspected bloodstream infections. Conventional clinical signs like fever, leukocytosis, or hemodynamic instability are nonspecific and may overlap with non-infectious inflammatory conditions or post-surgical responses. In such scenarios, PCT can assist in both initiating and more importantly, discontinuing antibiotics safely, thereby minimizing overuse.[20]

The PRORATA trial (2010) was a landmark multicenter randomized controlled trial involving 621 ICU patients. It demonstrated that a PCT-guided strategy significantly reduced the duration of antibiotic therapy by nearly 3 days (from 14.3 to 11.6 days) without increasing mortality or adverse outcomes. Importantly, patients in PCT group had a proven 23% reduction in antibiotic exposure compared to standard care, validating the biomarker's utility in guiding antibiotic discontinuation.[28] The SAPS (Stop Antibiotics on Procalcitonin guidance) trial, a large multicenter randomized study conducted across 16 Dutch ICUs with over 1,800 critically ill patients, demonstrated that daily procalcitonin (PCT) monitoring can safely reduce antibiotic duration without increasing mortality. In the PCT-guided group, antibiotics were discontinued when PCT levels fell below 0.5 ng/mL or dropped by ≥80% from peak values. This approach led to a significant reduction in antibiotic exposure (median 5 vs. 7 days) while maintaining non-inferior outcomes in both 28-day and 1-year mortality. Although the study noted challenges such as test costs and adherence variability, SAPS provided robust evidence supporting the use of PCT to optimize antimicrobial stewardship in ICU settings.[29]The Reduction in Antibiotic Duration in ICU Trials (PRORATA & SAPS) with PCT-Guided Stewardship is shown in **Figure 2.**

This bar chart compares the average duration of antibiotic therapy between standard care and PCT-guided protocols in two major randomized controlled trials: PRORATA and SAPS. The figure highlights the role of PCT in reducing unnecessary antibiotic exposure in ICU patients. (Bouadma et al. (2010) [26], de Jong et al. (2013) [27]).

Beyond sepsis, PCT has shown utility in ventilator-associated pneumonia (VAP) and post-operative infections. In VAP, where empirical broad-spectrum antibiotics are often used due to diagnostic uncertainty, PCT trends can guide early de-escalation or discontinuation of therapy. Studies have shown that incorporating PCT reduces unnecessary prolonged antibiotic exposure in intubated patients without compromising outcomes.[30] In surgical patients, post-operative inflammatory markers such as CRP and leukocytosis may persist even in the absence of infection, complicating clinical decision-making.[31] PCT, being more specific to bacterial infections, helps differentiate surgical inflammation from infection.[15] For example, in abdominal or thoracic surgeries, persistently low or declining PCT levels can reassure clinicians that post-

operative fever is likely non-infectious, reducing unwarranted antibiotic use.[29]

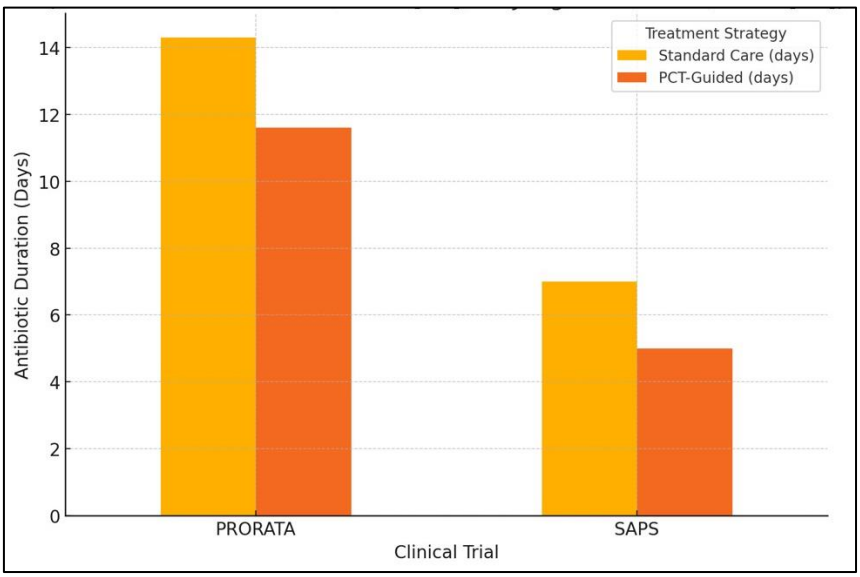

Figure 2: Reduction in Antibiotic Duration in ICU Trials with PCT-Guided Stewardship

Despite its utility, PCT should not be used in isolation. Clinical judgment, microbiological results, and imaging remain essential components of decision-making. PCT is most effective when incorporated into algorithms with predefined thresholds (e.g., <0.25 ng/mL for low likelihood of bacterial infection), and its serial measurement over days is more informative than a single reading.[32] When applied thoughtfully, PCT-guided strategies in ICUs have consistently demonstrated reductions in antibiotic overuse, shorter hospital stays, and potential mortality benefits.[33]

3.2 Emergency and Outpatient Settings

In emergency departments (EDs) and outpatient clinics, the indiscriminate use of antibiotics—particularly for self-limiting viral infections—continues to be a driver of antimicrobial resistance.[34] PCT serves as a rapid, actionable tool in these fast-paced environments to support targeted antibiotic use, especially for community-acquired pneumonia (CAP), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and upper respiratory tract infections (URTIs).[35]

For CAP, distinguishing bacterial from viral etiologies is critical to avoid unnecessary antibiotic exposure. Multiple randomized controlled trials and meta-analyses have shown that the antibiotic therapy guided by PCT can safely reduce antibiotic initiation and duration. A 2017 meta-analysis by Schuetz et al., which included over 6,700 patients across 26 trials, found that PCT-guided therapy resulted in a 2.4-day reduction in antibiotic exposure and lower risks of side effects without increasing treatment failure or mortality.[36] Similarly, in AECOPD, where infections are frequently viral or non-infectious, PCT can be used to withhold or stop antibiotics in patients with low levels. In one trial, patients in the PCT-guided group had significantly fewer antibiotic prescriptions (40% vs. 72% in standard care) and no compromise in clinical recovery.[37] These findings are particularly important given that inappropriate antibiotic use in COPD exacerbations can accelerate resistance and disrupt microbiota, compounding long-term health risks. In URTIs, including sinusitis, pharyngitis, and bronchitis, PCT has a lower but growing role. Although many of these infections are clearly viral, antibiotic prescriptions remain high. PCT testing can reinforce clinicians' confidence in withholding antibiotics. Rapid point-of-care testing—available within 15–20 minutes—is now feasible and increasingly cost-effective, making implementation in outpatient settings practical.

One barrier in emergency settings is logistical integration—clinicians must receive PCT results in real time to impact prescribing decisions. Thus, pairing PCT with clinical decision support systems (CDSS) or using it in walk-in clinics with high antibiotic prescribing rates may enhance its impact.[38] In summary, in outpatient and emergency care, PCT provides a bridge between evidence and action, empowering providers to reduce inappropriate antibiotic prescribing. It supports antimicrobial stewardship goals by reducing exposure, mitigating resistance development, and preserving antibiotics for patients truly in need.

3.3 SPECIAL POPULATIONS

While PCT is broadly useful, caution is required in special populations due to physiological or pathological conditions that can affect its interpretation. In immunocompromised patients, such as those undergoing chemotherapy or organ transplantation, PCT

kinetics may be altered. The baseline inflammatory response can be blunted, leading to false negatives, while other non-infectious triggers (e.g., graft-versus-host disease) may elevate PCT levels.[39] Despite these complexities, emerging evidence suggests that serial PCT measurements—rather than absolute values—can still provide useful trends, particularly for tracking response to therapy.[33]

Pediatric populations present additional challenges. Neonates, especially in the first 72 hours of life, may have physiologically elevated PCT levels, limiting its diagnostic accuracy for neonatal sepsis.[13,40] However, in older children with suspected bacterial infections, several studies have shown that PCT-guided therapy can safely reduce antibiotic duration, particularly in lower respiratory tract infections.[32] Yet, standardized thresholds and algorithms tailored to pediatric age groups are still being refined.[15]

Patients with chronic kidney disease (CKD) or those on dialysis may exhibit chronically elevated PCT levels due to reduced clearance or low-grade systemic inflammation.[16] In these patients, interpretation must be adjusted, and PCT should not be the sole determinant of antibiotic therapy. That said, trends remain valuable—declining PCT may still suggest infection resolution even when baseline levels are higher than in the healthy population.[17]

Overall, while PCT is a powerful tool, it must be used with clinical context and population-specific considerations. Evidence gaps remain in transplant recipients, patients with autoimmune diseases, and those with rare conditions, necessitating further research.[41] Until then, a cautious, algorithmic approach with attention to trends rather than static thresholds is advisable in special populations.

4. IMPLEMENTATION IN STEWARDSHIP PROGRAMS

4.1 How PCT is integrated into stewardship protocols

Based on the PCT kinetics level, the treatment algorithm may be developed as its levels correlate with bacterial infection severity, and thus it aids in starting, adjusting, withholding, or stopping antibiotics appropriately. In addition, the duration of antibiotic course could be decided by rechecking PCT levels at regular intervals.[42,43] PCT can be integrated into antimicrobial stewardship protocols as a biomarker to guide antibiotic therapy. However, the clinical judgment has an important role in conjunction with using PCT. The PCT-Guided Antimicrobial Stewardship Framework is depicted in **Figure 3.**

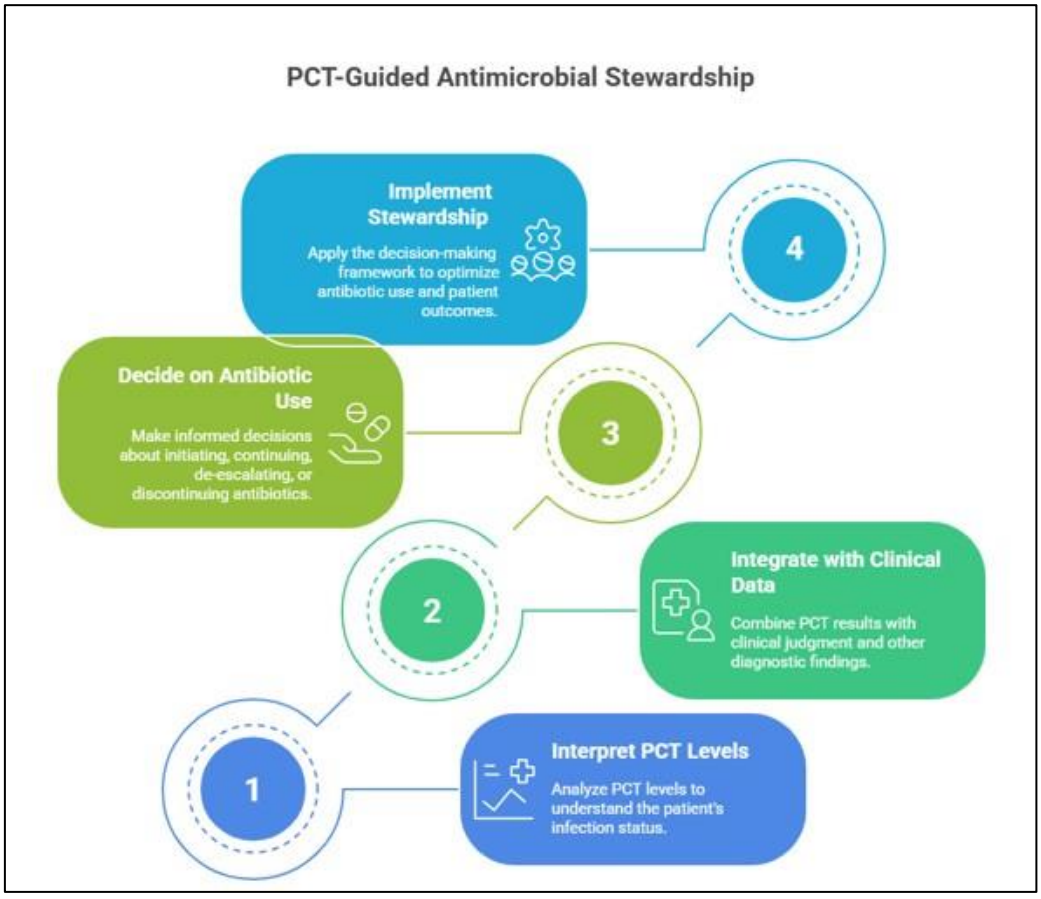

Figure 3: PCT-Guided Antimicrobial Stewardship Framework.

This visual outline a four-step clinical decision-making framework for utilizing Procalcitonin (PCT) levels in antimicrobial stewardship. Starting with interpreting PCT levels to assess infection status, the model integrates clinical data to contextualize findings, guides antibiotic use decisions such as initiation or discontinuation, and culminates in the implementation of stewardship interventions to optimize patient outcomes and reduce unnecessary antibiotic exposure.

4.2 Benefits observed in real-world hospital settings

The PCT biomarker has high sensitivity and specificity for bacterial infections, especially in lower respiratory tract infections (LRTIs) and sepsis. Thus, bacterial and viral infections can be distinguished via PCT-guided protocols, particularly in respiratory illnesses and sepsis. The PCT can be incorporated as part of sepsis protocols to support the diagnosis, monitor progression of disease, and guide empirical treatment.[44] PCT levels rise quickly (within 2–6 hours of bacterial infection), allowing for faster clinical decision-making to escalate or de-escalate antibiotics. It helps prevent antibiotic resistance and reduces side effects associated with broad-spectrum antibiotics.[43] In addition, during the recovery phase, it helps in deciding to discontinue the antibiotics. In some studies where PCT-guided protocols were implemented for sepsis, lower mortality rates and reduced hospital length of stay were reported.[42]

4.3 Barriers: clinician trust, cost, access

Clinicians are used to relying on traditional markers (e.g. CRP, WBC) or clinical judgment and distrust PCT as a sole or primary decision-making tool, especially in complex patients. Additionally, insufficient training for clinicians and uncertainty on how to interpret and act on PCT results are a major challenge in immunocompromised patients, localized infections, or non-infectious inflammatory conditions.[41] In most of the clinical settings, the equipment for testing PCT is not available, and reliance on send-out labs delays results, reducing clinical usefulness. In a study conducted by Kip et al.,2015, the cost of PCT measurement was recorded high (€ 31.71) in comparison to the CRP (€ 4.19) and leukocyte count (€ 1.85) tests. [45] Expensiveness and consistent access to testing kits and reagents can be disrupted in resource-limited settings.[25,27]

4.4 Brief note on relevant guideline recommendations (SSC, NICE, IDSA)

As per the Surviving Sepsis Campaign (SSC) and Infectious Diseases Society of America (IDSA) guidelines, PCT alone is not recommended to guide initiation of antibiotics in sepsis or septic shock. PCT is considered an adjunct, not a replacement for clinical judgment on initial antibiotic decisions. However, PCT can be used to support the discontinuation of empiric antibiotics in sepsis when there is evidence of clinical improvement.[4,46] As per the National Institute for Health and Care Excellence (NICE) guidelines, PCT is not routinely recommended for guiding empirical treatment in sepsis due to limited cost-effectiveness and insufficient evidence for impact on clinical outcomes.[47] While European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend that the PCT can be a valuable tool in EDs for guiding antibiotic initiation and duration, especially in patients with suspected LRTI/acute exacerbation of asthma and AECOPD who are likely to be admitted to the hospital.[48] However, in all four guidelines, the clinical assessment and risk stratification remain the cornerstone and recommend integrating PCT with clinical judgment and other diagnostics.

5. CONCLUSION AND FUTURE PERSPECTIVES

5.1 PCT is a valuable tool but not standalone

PCT has proven to be a valuable tool in antimicrobial stewardship, aiding in the differentiation of bacterial from viral infections and guiding antibiotic initiation and discontinuation. However, PCT is not a standalone diagnostic tool. Its interpretation must be integrated with clinical judgment, patient context, and other diagnostic findings. Its use across ICU, emergency, and outpatient settings has been allied with reduced antibiotic exposure, shorter hospital stays, and improved clinical outcomes without increasing mortality.

5.2 Potential for broader implementation with improved awareness and access

With improved awareness, clinician training, and access to rapid testing—particularly in resource-limited settings—PCT has strong potential for broader implementation. Future directions include integrating PCT into clinical decision support systems and conducting more research in special populations and co-infection scenarios. When used thoughtfully, PCT can play a significant role in combating AMR and promoting rational antibiotic use.

5.3 Best used with clinical judgment and stewardship frameworks

Despite its strengths, barriers such as cost, limited access in low-resource settings, and clinician hesitancy remain. PCT should not replace clinical judgment but rather complement it within well-defined protocols.

5.4 Brief note on emerging trends or future research needs

Future research should focus on refining PCT thresholds for special populations, such as neonates, immunocompromised patients, and those with chronic inflammatory conditions. The role of PCT in viral-bacterial co-infections (e.g., COVID-19) and its integration with artificial intelligence and clinical decision support systems (CDSS) are promising areas. Additionally, the development of affordable point-of-

care PCT tests could expand access in low-resource settings, supporting global stewardship efforts.

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Dr. Ntsoaki Betty Mopane designed the concept, conducted the literature review, and drafted the manuscript. Dr. Faiza Parveen Baloch provided critical revisions and approved the final version. Both authors contributed equally to the development of the article.

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