Review Article

A mini-review of point-of-care C-reactive protein testing in sepsis in the Emergency Department

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Article Info

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Abstract

Timely initiation of appropriate treatment of sepsis in the Emergency Department is crucial in a patient's prognosis. Surviving Sepsis Campaign guidelines suggest improved results in septic shock where antimicrobials are given within 1 hour of presentation. The recognition and treatment of critically ill patients could be expedited using different methods of point-of-care testing as opposed to centralised laboratory testing. C-reactive protein is utilised as a predictor for sepsis prognosis and should be interpreted in conjunction with patient clinical findings due to its low specificity and sensitivity. Some efficient and simple C-reactive protein point-of-care assay kits discussed include immunoturbidimetry, immunonephelometry, lateral flow assays and bioassays, which have advantages over laboratory-based methods, but still require further investigation. A useful tool such as a C-reactive protein point-of-care test could potentially enhance the operational performance of emergency care. Its use in optimizing antibiotic therapy to curb the rate of antimicrobial resistance and improve sepsis outcomes still requires validation. Septic shock management in the Emergency Department continues to be a challenging task and future verification studies and clinical guidelines on biomarkers for point-of-care testing are required to establish its reliability.

Introduction

The Emergency Department (ED) is generally an environment with a high volume of patients and often prolonged waiting times which can impact patient care. There is an increasing need to enhance patient flow through the ED to improve patient outcomes and avoid overcrowding.

Point-of-Care has become increasingly significant in fast-paced settings where timely treatment is essential [1]. Using POC testing, the delay between the onset of symptoms and commencing the relevant therapy could be significantly reduced, although there is not enough evidence available to support this [2]. This could be consequential in critically ill patients, such as in sepsis, where the time of initiation of antibiotics predicts the patient's prognosis and progression to septic shock [1,3,4,5]. Sepsis is an uncontrolled systemic response to an infection resulting in multiple organ dysfunction and sometimes death [6,7]. Aiming to prescribe broad spectrum antibiotics within one hour of presentation reduces mortality according to the Surviving Sepsis Campaign guidelines and the Sepsis 6 pathway, an adaptation of these guidelines [5,8].

To classify acutely ill patients, C-reactive protein (CRP) can be used where the intensity of the pathology is directly proportional to the CRP level in the bloodstream [4,9]. POC CRP testing may expedite triage and streamline ED care [1]. Although this biochemical marker has a low specificity, it has shown to be effective in reducing inappropriate antibiotic prescribing [9]. Despite simple assay availability such as immunoturbidimetry, immunonephelometry and lateral flow tests which may be used under POC conditions, the non-quantitative CRP value and high analytical sensitivity remain an issue [4]. Gaps in verification studies and clinical guidelines currently prevent its clinical use as a POC test [1,4,9].

Diagnosctic value of CRP in Sepsis

C-reactive protein is an immunochemical marker of infection, as well as inflammatory conditions and cardiovascular events, which is predominantly synthesised by the liver [8,10,11,12]. This acute-phase protein rises within 4-6 hours of a stimulus and doubles every 8 hours with a peak at 36-50 hours [9]. This CRP surge during an infection is a response to monocytic mediators known as Interleukin-1 and Interleukin-6 (IL-6). Subsequently, the binding of CRP with phosphocholine activates the complement pathway and has a protective function against bacterial infections [4,12].

Clinical decision making may be guided by CRP levels which can be particularly useful in differentiating between bacterial and viral infections [4]. However, due to the low sensitivity and specificity of CRP testing, interpretation in conjunction with the patient's history and clinical examination is paramount [11,13,14,15]. A prompt and more specific biomarker for sepsis is procalcitonin (PCT) which rises in 3-4 hours after a stimulus [13,15,16]. PCT can predict the patient's prognosis and is valuable in analysing the response to antimicrobials. Although this biomarker can substantially improve the clinical management of sepsis, there are still limitations in reliability. The use of PCT guided antibiotic management for sepsis in adult patients may not be cost-effective in all settings [11,15,16].

Point-of-Care vs Laboratory Based Testing

POC testing is defined as medical testing at or near the site of patient care which allows for rapid result turnaround times (TAT) and therefore, quicker decision making [17,18,19,20]. This is essential in an Emergency care setting where early diagnosis and treatment predicts the outcome of the patient. Typically, the TATs for routine ED blood results processed in a centralised laboratory are estimated to be over 1 hour, whereas POC testing may take between 10-15 minutes [17]. POC methods may therefore minimise diagnostic ambiguity and result in more rational antibiotic prescribing in critically ill patients [17,18]. From patient presentation, sepsis progresses to septic shock by 8% for each hour that antimicrobials are withheld [3]. According to the Surviving Sepsis Campaign Guidelines and the Sepsis 6 pathway, broad-spectrum antibiotics initiated within 1 hour of the recognition of septic shock resulted in improved patient outcomes [8,21]. Process streamlining is vital to be able to take advantage of the expedited results from POC testing. The reduction in TATs can improve patient flow through the ED and could result in a shorter length of stay, contributing to a more efficiently functioning department, however the impact on patient safety still needs to be studied [22].

Point of Care Methods and Operational Considerations

A routine method of measuring serum or plasma CRP, performed under POC conditions and with laboratory analysers, is by immunoturbidimetry. This CRP kit is cost-efficient and simple to use, measuring the interaction between an antibody and an antigen by changing the solution turbidimetry. This assay is cost efficient and although it has a lower sensitivity compared with laboratory-based immunonephelometric assays, it still produces similar results. However, immunoturbidimetric methods require an analytical device which may incur errors on operation. Immunonephelometric assays are complex laboratory tests which are more costly than immunoturbidimetry. They require powerful light sources and therefore are less favoured in comparison [4]. Another simple POC method includes a colourimetric disposable analytical device involving easily accessible resources and minimal reagents, known as the lateral flow test [4,23]. Most lateral flow assays are only qualitative and not economical per test performed as opposed to Enzyme-linked immunosorbent assay (ELISA) and chemiluminescent immunoassay (CLIA) under laboratory conditions. Both immunoturbidimetric and lateral flow assays are typically available within 15 minutes, nevertheless these methods are not yet practical in a POC setting. Using traditional methods, the sensitivity of current ELISA test kits is between 2 and 40ng/L and the limit of detection can reach about 5ng/L. CLIA test

kits have an increased sensitivity of 5ng/L and the test range is estimated to be between 10ng/L and 10µg/L compared to ELISA. Other kits with lower sensitivities and higher detection ranges exist [4].

The development of new user-friendly biosensors and bioassays may compete with laboratory methods, such as ELISA, in terms of accuracy and sensitivity in POC conditions [4,24]. They apply improved analytical specifications for recognizing moderate risk pathologies with a typical threshold of 1mg/L. Assays with light reflectance spectroscopy involving immobilized anti-CRP antibodies had a dynamic range for CRP equivalent to 0.05-200mg/L and limit detection of 1µg/L [4]. A study by Mou et al., 2020 on the detection of infection in the ICU with a newly developed dynamic multiplex POC CLIA was performed. The multiplex included CRP, PCT and Interleukin-6 (IL-6) and showed a sensitivity of 91.7%, 94.4% and 91.6% respectively and a specificity of 63.1%, 81.2% and 66.7% respectively. The cut-off values were 5µg/ML for CRP, 0.2ng/mL for PCT and 50pg/mL for IL-6. This study demonstrates the significance of utilising biomarkers in combination for detecting infection in a clinical setting. [23]

The World Health Organisation states that the development of new POC devices need to meet the ASSURED guideline criteria, which aims for affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable test results to the end-user [19]. POC CRP testing needs further refining due to reduced sensitivity, test TAT and the non-quantitative CRP concentration as a result of its simplicity. Limited published validation studies exist on the performance of these CRP POC assays [4].

Table 1: POC vs Laboratory based simple kit testing methods.

Methods	Estimated TAT (minutes)	Benefits	Limitations
POC			
Immunoturbidimetry [4]	5-15	**AP**: Quantification of values; Similar outcomes to immunonephelometric methods **CP**: Simple to use **Other:** Cost efficient	**AP**: Requires an analytical device **CP**: User-errors
Lateral Flow [4,24,25]	20	**AP**: Easily accessible resources with minimal reagents; No analytical device needed **CP**: Simple to use	**AP**: Reduced analyte concentrations; Inability to conduct a multi-step analysis **CP**: Reduced clinical sensitivity and specificity compared to ELISA due to capillary flow rate; Only qualitative **Other**: Average cost per reagent and chemical is equivalent or more than one ELISA well plate
Biosensors and bioassays [4,25]	2-20	**AP**: Improved accuracy **CP**: Improved sensitivity; Wearable	**AP & CP**: Still in development
Laboratory-based			
ELISA [4]	90-1440	**AP**: Quantification of values **CP**: High sensitivity **Other**: Inexpensive kits	**AP**: Complex analytical process; Professional staff required **AP & CP**: Increased TAT
CLIA [4]	90-1440	**AP**: Quantification of values **CP**: Increased sensitivity compared to ELISA	**AP**: Laboratory based **AP & CP**: Increased TAT

TAT=turn-around time, POC=point-of-care, AP=analytical performance, CP=clinical performance, ELISA=enzyme-linked immunosorbent assay, CLIA=chemiluminescent immunoassay

Limitations and Special Situations

Differentiating between sepsis and non-infectious systemic inflammatory response syndromes is challenging [26]. CRP can be significantly influenced by age, body mass index, cholesterol levels, blood pressure, vigorous exercise, smoking status and heat stroke [4,9,12]. Other conditions such as surgery, burns, trauma, tissue necrosis, advanced cancer, crystal-induced arthritis and auto-immune disorders contribute to the high false-positive rate of CRP [4,9]. In immunosuppressed patients, serum CRP levels have a low specificity for diagnosing bacterial infections which may lead to delayed interventions [27,28].

Although POC testing is convenient and minimises the TAT from testing to treatment, there are shortfalls in analytical accuracy and reliability. Establishing a Quality Management System is essential as actions usually occur immediately after POC testing without verification.

Quality assurance measures and regular calibration need to be implemented to avoid inaccurate values, ensuring no harm is done to the patient. There are no evidence-based guidelines for quality control in POC testing which further limits its use [29,30,31].

A Health Technology Assessment done by the Health Information and Quality Authority (HIQA), 2019, assessed POC CRP testing in acute respiratory tract infections to guide antibiotic prescribing in primary care. The diagnostic test accuracy had mixed evidence for pneumonia and lower respiratory tract infections with a cut-off value of 100mg/L to rule in infection. This was not accurate in ruling out pneumonia using a cut-off value of 20mg/L. HIQA suggested the use of CRP POC testing in combination with clinical history and examination to potentially improve clinical judgement specificity. The analytical performance of two Conformité Européenne (CE) marked semi-quantitative devices were reviewed. This revealed that the accuracy of the tests was moderate to good but decreased after 5 minutes of the reading. In laboratory conditions, most of the CRP POC CE marked devices were accurate. Variations in accuracy and precision were found when the same tests were used in primary care suggesting the need for relevant training and strict standardised operating procedures [32]. Healthcare workers and other device operators should receive professional training in quality assurance processes to ensure result consistency [29,32,33]. Implementing regular internal quality control and utilising devices with less pre-analytical handling are associated with increased accuracy. POC CRP testing was more cost-effective than clinical judgement alone. There is limited evidence on its use in the ED [32].

POC CRP tests have an EU Regulatory requirement on In Vitro Diagnostic Devices (IVDR). Products with CE markings ensure conformity with the regulations. This provides more precise product and clinical data requirements, improved device surveillance, traceability and increased monitoring by authorities [32].

The CRP biomarker is more frequently used due to its wider availability as opposed to PCT, however this should not be used as a standalone biomarker for sepsis triage or therapeutic decision making. Biomarkers have some value in a patient's prognosis, although their independent use is still limited [26]. Utilising CRP as a tool for antibiotic therapy optimisation can be associated with a reduction in unnecessary antibiotic exposure in critically ill patients [32,34]. For more precise results, a combination of biomarkers may potentially be required for sepsis prognosis, and this would necessitate further investigation and guidelines [13,26].

Other Biomarkers in Sepsis

Biomarkers in the ED are generally favoured to develop a prompt diagnosis, formulate differential diagnoses and enhance patient care. POC tests are preferred due to time-sensitive decisions; however, there are still concerns over false-positive results, limited availability and the costs per test [35].

CRP and PCT are familiar biomarkers with diagnostic value in infection. PCT is predominantly assessed using an immunofluorecent assay [36]. It rises 4 hours after a bacterial infection which precedes that of CRP and may be more effective in the detection of early sepsis. Despite its increased specificity compared to CRP, optimal cut off levels still need to be established and its higher costs should be considered [36,37,38,39]. PCT has been more distinctive in determining an infective process over an inflammatory one as opposed to CRP and White Blood Cell counts (WBC). This can guide the correct administration of empirical antibiotics and reduce the total duration of antibiotic therapy although its specific use in the ED was unclear [36,40,42].

Other biomarkers such as IL-6, Blood Urea Nitrogen (BUN) and Presepsin have also been studied. Within only 2 hours of the onset of infection, IL-6 levels increase rapidly. It has been shown to be a more superior diagnostic and prognostic tool in early sepsis than PCT [41,42]. CRP is mostly produced in response to IL-6 and is therefore dependent on the latter. Like CRP, this biomarker is affected by inflammatory conditions such as rheumatoid arthritis and active cancer. As a sole biomarker, it may not accurately diagnose bacterial infections [43].

BUN is a liver by-product of protein metabolism which is filtered by the renal system. Elevated BUN levels are seen with renal organ dysfunction and can be an indicator of early sepsis [41].

Presepsin is a soluble form of lipopolysaccharide CD-14 which is expressed on monocytes, macrophages and dendritic cells. It rises within 2 hours of infection and is valuable in excluding sepsis. It is more sensitive than PCT and CRP in predicting disease prognosis, however there is insufficient data to support its use in the ED [37].

Over-reliance on CRP alone can lead to unnecessary antibiotic administration, especially in the first 12 hours of infection [44]. A definitive diagnosis requires multiple tests including a combination of biomarkers with blood cultures, Polymerase Chain Reaction tests and antibody detection assays where applicable [36,40,44].

Table 2: Biomarker diagnostic performance in bacterial infections.

Study	Year	Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC (95% CI)
Ramakrishnan V et al. [40]	2025	CRP PCT WBC	92.86 69.23 92	7.5 57.14 62.79	80.06 88.04 93.34	20.792 28.96 58.07	42.65 61.76 73.5	0.517 0.5 0.631
Nargis W et al. [36]	2014	CRP PCT	85.45 76.36	33.3 72.2	79.66 89.36	42.86 50	72.6 75.34	- -
Harsoor V et al. [39]	2024	CRP PCT	78.9 85.6	71.2 81.3	83.4 90.2	63.5 75.5	- -	0.80 0.89
Yu B et al. [41]	2022	IL-6 BUN	68.3 48.9	82.8 86.4	- -	- -	- -	0.764 0.696
Bruhn R et al. [43]	2025	CRP PCT IL-6	68.1 72 75.3	78.5 67.5 67.5	93.4 91.1 92.4	35.5 34.2 38.3	- - -	0.79 0.76 0.77
Orfanos I et al. [45]	2024	CRP ≥20 mg/L IL-6 ≥50 ng/L	76 93	89 66	55 33	95 98	- -	0.87 0.82

PPV=positive predictive value, NPV=negative predictive value, AUC=area under the curve, CI=confidence interval, CRP=c-reactive protein, PCT=procalcitonin, WBC=white blood cells, IL-6=interleukin 6, BUN=blood urea nitrogen

Clinical Impact and Outcomes

Delays in identifying severe sepsis and septic shock is related to an increased rate of morbidity and mortality. During triage in the ED, a patient with sepsis may initially present as normotensive and with non-specific symptoms and so sepsis could be missed in the first instance [34]. Multiplex biomarker POC testing may more rapidly identify or confirm sepsis prior to receiving laboratory-based results [1,23,34]. This could improve patient outcomes although there are limited POC guidelines to support the administration of antibiotic therapy in the ED [1,34]. Following appropriate POC training and process optimization, streamlined patient care can be implemented in the ED, and therefore a potentially reduced length of stay although limited data is available on this [22, 46].

Laboratory-based testing has an increased TAT, require more staff and costly equipment, yet remains the gold standard for accurate results. Even though POC biomarkers have a high initial cost, they offer bedside testing with reduced TAT and allow for rapid clinical decision making. This may outweigh traditional methods by improving patient waiting times, minimising the duration of hospital stay and overall, more cost effective [47].

According to a study group from the European Society of Clinical Microbiology and Infectious Diseases, antimicrobial stewardship (AMS) guidance tailored for the ED is lacking [48]. The aim of AMS is to responsibly prescribe antimicrobials to enhance patient outcomes, therefore minimising antimicrobial resistance due to its improper use. A considerable number of patients initiated on antibiotics in a hospital setting are seen through the ED which are often resumed as an inpatient [34,48,49]. Biomarker-guided antibiotic therapy has the potential to reduce the overprescription of antimicrobials to patients [34,48,49,50]. Therefore, POC CRP-guided treatment may form part of AMS in the ED to help minimize the threat of antimicrobial resistance particularly in lower respiratory tract infections, although there is minimal evidence available to support this [48,49,51].

Conclusion

CRP is a non-specific biomarker which has its own pitfalls and should be used in conjunction with the clinical history and examination of the ED patient instead of an investigation in isolation. CRP has a low specificity for sepsis compared to non-infectious inflammatory conditions and identification of early sepsis is restricted. Other biomarkers such as PCT or a multiplex of biomarkers may be more favourable in this regard. While limited developments, guidelines and mixed evidence are available for POC CRP testing in sepsis management, this method offers the potential to enhance the operational performance of the ED rather than improve diagnostic precision.

Declaration of Conflict of Interests

I, Natasha Gomes Berlouis, declare that I have no conflicts of interest related to this mini-review. I have not received financial support or other benefits from organizations that may influence the interpretation or conclusions of this mini-review.

Ethical Approvals

No human subjects were involved in this mini-review. All data discussed is obtained from and available in the published literature and studies cited in the references.

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Natasha Gomes Berlouis: Conceptualization, Methodology, Investigation, Resources, Writing-Original Draft, Writing-Review & Editing, Visualization, Project Administration.

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