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Diagnostic Uncertainty in Early Sepsis: how Current Biomarker Limitations Propagate Misclassification Risk in Emergency Care

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ABSTRACT

Sepsis is one of the most lethal conditions encountered in emergency care, with hospital mortality ranging from 20-40% in septic shock, and 11.5% of patients dying within the first 72 hours of presentation. Early presentations are heterogeneous, rapidly evolving, and often accompanied by nonspecific biomarkers, often leading clinicians to make high stakes decisions before definitive diagnostic information is available. In this critical window, distinguishing between bacterial, viral, or non infectious etiologies determines triage acuity, antimicrobial initiation, and monitoring intensity.

The biomarkers used to anchor these early decisions—C-reactive protein (CRP), procalcitonin (PCT), lactate, and leukocyte count—are physiologically limited. These tools quantify downstream inflammatory byproducts, meaning they may remain normal in early bacterial infection, rise in non infectious conditions, and overlap substantially across bacterial and viral illnesses. These limitations create structural diagnostic uncertainty at first contact.

Misclassification in this window has cascading consequences: delayed antibiotics for bacterial sepsis, unnecessary antimicrobial exposure for viral etiologies, propagation of antimicrobial resistance, and the destabilization of emergency department (ED) workflow through triage distortion, resource misallocation, and safety critical delays. This review synthesizes the biological constraints of current sepsis biomarkers and the operational realities of emergency care, highlighting the need for supplemental diagnostic strategies capable of resolving early diagnostic uncertainty through alternative mechanisms.

Keywords

Biomarkers, Diagnostic Uncertainty, Emergency Department, Sepsis misclassification.

Introduction

Early sepsis care in the emergency department (ED) is shaped by profound diagnostic uncertainty. Clinicians must rapidly determine whether an acutely ill patient is experiencing a bacterial, viral, or non-infectious cause, yet early presentations are often nonspecific, rapidly evolving, and lack definitive clinical cues. This initial sepsis phenotype assignment—bacterial or viral—anchors clinical reasoning, determines triage level, antibiotic initiation, and influences resource allocation during the most time-sensitive phase of care. Because phenotype models remain unstable across cohorts, incorrect early assignment can place patients on suboptimal clinical trajectories, risking delayed antibiotics, unnecessary antimicrobial exposure, missed deterioration, and downstream operational strain [1].

A central driver of this uncertainty is the limited performance of traditional sepsis biomarkers. C-reactive protein (CRP), procalcitonin (PCT), lactate, and leukocyte count quantify downstream inflammatory byproducts rather than the upstream immune programs that distinguish bacterial from viral infection [2,3]. CRP and PCT rise in numerous non-infectious conditions—including trauma, autoimmune disease, major surgery, and

cardiogenic shock—while lactate reflects hypoperfusion rather than etiology. Subsequently, Leukocyte counts may remain normal early in infection or appear blunted in immunocompromised patients. In the ED, these nonspecific signals can lead clinicians to incorrect diagnoses when biomarkers are elevated for unrelated reasons, offering little support for early bacterial or viral discrimination.

These gaps manifest as measurable misclassification in early ED care. Misdiagnosis is common, with overall ED diagnostic error rates estimated around 10–15%. Sepsis-specific misdiagnosis occurs in roughly 17% of cases by the 15-minute mark, and in 8% of cases by the 1-hour mark, where symptoms overlap broadly with other inflammatory and hemodynamic conditions [4,5]. When clinicians incorrectly label bacterial illness as viral, this can cause antibiotic delay and increased mortality, while labeling viral illness as bacterial drives unnecessary sepsis evaluations and contributes to antimicrobial resistance [6]. These early decisions shape the entire care pathway, often before definitive diagnostic information is available. Considering these early decisions shape the entire care pathway, biomarker-driven uncertainty becomes the root cause of downstream clinical and operational harm. In cases of sepsis, this pathway is crucial, as in-hospital mortality rates soar from 20-40% [7], thus reinforcing the importance of correct misclassification early in sepsis development.

This review evaluates the physiological limitations of current sepsis biomarkers, examines how these limitations contribute to early sepsis misdiagnosis, and analyzes the clinical and operational consequences that arise when infectious phenotypes are incorrectly assigned. By focusing on real-world ED workflows and the constraints of existing diagnostic tools, this review highlights the structural challenges that shape early sepsis management and underscores the need for diagnostic strategies capable of reliably identifying infectious phenotypes at the point of initial assessment.

Limitations of Current Biomarkers

Early diagnostic decision-making in the ED relies upon on biomarkers that are not structurally capable of distinguishing bacterial from viral or non-infectious etiologies. The tools most used at first contact—CRP, PCT, lactate, and leukocyte count—are physiologically incapable of determining sepsis phenotype during the critical early hours of illness. Their limitations arise from a shared structural problem: each measures downstream inflammatory byproducts, which cannot accurately identify infection class, though clinicians often rely upon them for judgment. As a result, these biomarkers may provide false alarms or assurances when elevated, generating diagnostic uncertainty that propagates through ED care.

CRP: Slow Kinetics and Broad Specificity

CRP is one of the most frequently ordered biomarkers in the ED to mark sepsis, yet it is fundamentally nonspecific in type determination. CRP rises in trauma, autoimmune disease, malignancy, chronic inflammatory conditions, sterile injury, and viral illness—conditions commonplace in emergency care [3]. Because CRP reflects generalized inflammatory activation rather than pathogen-specific immune programs, it often misleads clinicians at the bedside.

CRP's slow kinetics further undermine its utility. CRP is synthesized in the liver in response to IL-6 signaling, a process requiring several hours to initiate. Levels often remain normal for 12–24 hours after infection onset, delaying recognition of bacterial illness and providing false reassurance during the earliest and most clinically consequential phase of care [3,8]. Multiple studies found that admission CRP levels do not reliably distinguish bacterial from viral infection, with only CRP velocity showing improved discrimination at best [3,8]. Additionally, meta-analysis assessed CRP maintained high false positive rates, at 44.3%, with high heterogeneity across sepsis cases [8], thus indicating CRP ambiguity. As such, when clinicians rely on CRP to determine sepsis phenotype, its nonspecific behavior can mislead early clinical reasoning, causing viral infections to be mislabeled as bacterial and resulting in unnecessary antibiotic exposure.

In sepsis cohorts, CRP sensitivity and specificity often fall in the 60–70% range, underscoring its limited discriminatory value [9]. A 2024 analysis of CRP dynamics demonstrated that CRP increases across a wide range of acute inflammatory states—including sterile inflammation—confirming that CRP reacts more broad inflammation than to infection class [10]. Even when paired with viral response markers such as Myxovirus resistance protein A (MxA), CRP has shown utility only in acute respiratory infections such as influenza, RSV, SARS-CoV-2 [11] and remains unvalidated for broader ED presentations such as sepsis, urinary infection, meningitis, or intra-abdominal infection. This narrow applicability reflects CRP's fundamental limitation: when only capable of measuring broad downstream inflammation, it becomes unreliable for sepsis diagnostic accuracy.

Procalcitonin: Insufficient for Clinical Detection of Sepsis

PCT is often considered a more specific and rapid diagnostic biomarker for the detection of bacterial infections in cases such as sepsis; however, ED data consistently reinforces its lack of reliability in aiding early diagnostic decisions and treatment courses.

Although host PCT production is mechanistically linked to bacterial toxin exposure, its behavior in acute care is heavily influenced by non-infectious physiologic stressors. Detectable PCT levels rise in trauma, surgery, cardiogenic shock, renal dysfunction, and other inflammatory or stress states—conditions common among ED patients. These non-infectious elevations undermine PCTs' supposed specificity for bacterial infection, leading clinicians to overinterpret PCT as a bacterial signal even when infection is absent [12].

Equally problematic, PCT frequently remains low in the early phase of bacterial sepsis, with at least 12-24 hours needed to

identify detectable levels [2]. PCT is thus considered unreliable during the critical first hours when clinicians must decide whether to initiate antibiotics. A recent multicenter study found that no PCT threshold reliably distinguished bacterial from viral etiologies in community-acquired pneumonia—a disease course consistent with sepsis progression—performing worse than clinician judgment alone [2,13]. Further evidence reinforces this limitation; a 2023 systematic review concluded that PCT demonstrates only moderate diagnostic accuracy for sepsis in ED populations and thus is considered an unreliable standalone decision tool [13].

As a result, PCT cannot reliably support early bacterial–viral differentiation or sepsis detection and must be considered part of the broader failure of current biomarkers to provide the diagnostic clarity acute care requires.

Lactate and Leukocyte Count

Lactate and leukocyte count are deeply embedded in ED workflows, yet neither provides meaningful information about infection type. Lactate is frequently used to assess severity in suspected sepsis, but it reflects tissue hypoperfusion and metabolic stress rather than pathogen class. Rising in dehydration, seizures, cardiogenic shock, hepatic dysfunction, and circulatory failure, lactate biomarkers strongly present across diverse and nonspecific ED presentations [14]. Even when paired with other biomarkers, a 2020 multicenter ED cohort revealed that lactate combined with qSOFA improved 28-day mortality prediction, but, like other lactate-based tools, predicted only severity rather than infection etiology, offering no direct information on pathogen class [14].

Leukocyte count is equally nonspecific. High counts are frequently encountered in early sepsis, lowered in immunocompromised patients, and elevated in stress, steroid exposure, trauma, or chronic inflammation. A 2020 critical care database analysis demonstrated that leukocyte count had poor predictive value for bloodstream infection [15], indicating worse performance than other biomarkers, and offering limited diagnostic discrimination in ED patients.

Collective Impact

The holistic limitations of common biomarkers thus create a structural diagnostic gap in emergency care. CRP, PCT, lactate, and leukocyte count quantify downstream inflammatory injury rather than providing signatures that distinguish bacterial from viral infection. Their lack of specificity, slow kinetics, and susceptibility to confounding make them unreliable anchors for early sepsis phenotype assignment. In the ED—where clinicians must rapidly determine infectious phenotype to guide triage level, antimicrobial initiation, and monitoring intensity—these limitations generate uncertainty that directly contributes to misclassification. Early typing errors then propagate through treatment decisions, stewardship practices, and operational flow, shaping patient trajectories long before definitive diagnostic information becomes available.

Consequences of Misclassification

Early sepsis phenotype assignment directly influences downstream clinical trajectories, carrying profound consequences for patient outcomes, antimicrobial exposure, and ED operations if a misclassification is made. Once clinicians misclassify bacterial illness as viral—or viral illness as bacterial—the treatment pathway diverges strongly from a biologically correct course. Incorrect bacterial labeling delays antibiotics and increases the risk of deterioration, while incorrect viral labeling drives unnecessary antimicrobial exposure and broad-spectrum initiation. These misclassifications distort the timing, appropriateness, and intensity of treatment courses, directly leading to downstream patient harm in the critical early hours of care. These errors can then freely propagate through both clinical outcomes and lead to population-level effects.

Delayed Antibiotic Administration

Timely antibiotic administration remains one of the most effective interventions for improving survival in bacterial sepsis, but diagnostic misclassification in the ED frequently postpones treatment. When bacterial illness is mistaken for viral or non-infectious conditions, patients lose access to the narrow therapeutic window in which antibiotics are most effective. With each hour of antibiotic delay increasing mortality by 7–10% [5,16], early recognition becomes essential for interrupting the inflammatory cascade that drives organ dysfunction and eventual sepsis.

In high mortality infections, this detriment becomes clear. In bacterial meningitis, delays of merely two hours double mortality risk, with each subsequent hour compounding odds of death [16,17]. Similar patterns are observed across pneumonia, urinary tract infections, septicemia, and intra-abdominal sepsis, where early antibiotics consistently correlate with improved survival, shorter hospital stays, and reduced need for invasive interventions. Conversely, delays in antibiotic treatment allow the inflammatory cascade to progress, increasing the likelihood of septic shock, leading to disseminated intravascular coagulation, acute respiratory distress syndrome, and irreversible organ failure [18]. Collectively, these findings demonstrate that biomarker-driven misclassification toward viral illness shifts life-saving therapy outside the optimal window, establishing delayed antibiotics as a cornerstone of preventable sepsis mortality.

Inappropriate Antibiotic Usage

Misclassification frequently leads to unnecessary antibiotic exposure, particularly when viral infections are incorrectly treated as bacterial. National surveillance data continues to show high rates of inappropriate antibiotic use for viral respiratory illnesses—which are highly capable of progression to sepsis. A 2021 JAMA Network Open analysis found that 55.9% of antibiotic prescriptions for respiratory conditions were unnecessary and unsupported by medical data, with inappropriate prescribing rates as high as 79.5% in community-acquired pneumonia cases [19,20]. In ED cohorts specifically, inappropriate antibiotic

initiation occurs in 27.6% of overall viral presentations [21]. Too often, emergency care clinicians are forced to initiate antibiotics when lacking a complete diagnostic framework, using treatment as a failsafe against the possibility of early bacterial sepsis. As a result, patients receive antibiotics that provide no clinical benefit and instead incur additional risks, including drug toxicity, allergic reactions, and treatment-related complications.

Misclassification also destabilizes clinical decision-making. When biomarkers inaccurately suggest a bacterial trajectory, clinicians may escalate unnecessarily—ordering serial lactates, initiating sepsis bundles, or admitting patients for IV therapy—all actions that divert resources from truly bacterially septic patients [20]. Alternatively, when bacterial infections are mislabeled as viral, clinicians may under-triage, delaying antibiotics and forcing later rescue interventions that are more labor-intensive and less effective. These stewardship failures increase clinician workload, raising interventions by 2-3-fold. Inappropriate antibiotic initiation requires additional reassessment, documentation, and follow-up, a pattern consistently demonstrated across ED and ICU stewardship studies [21].

The downstream effects of inappropriate antibiotic exposure also increase the risk of adverse drug events, which occur in up to 20% of ED antibiotic prescriptions—including nephrotoxicity, C. difficile infection, and severe allergic reactions [22]. Together, this data demonstrates how biomarker-driven misclassification directly increases unnecessary antibiotic use, clinician workload, and patient risk.

Antimicrobial Resistance

Inappropriate or delayed antibiotic exposure also creates selective pressures that accelerate antimicrobial resistance (AMR). When viral illness is treated with antibiotics, susceptible bacteria are eliminated while resistant strains expand. Conversely, when bacterial infections are missed or treated late, partially resistant organisms survive and proliferate. Together, these opposing misclassification errors reshape microbial populations at both the patient and population level, serving as the central driver of the growing AMR crisis globally [23].

Mechanistic analyses demonstrate that horizontal gene transfer—including plasmids, integrons, and transposons—is a major accelerator of resistance spread across microbial communities [24]. These processes are amplified by antibiotic-induced disruption of the gut and respiratory microbiome, which weakens colonization resistance and enables organisms such as ESBL-producing Enterobacterales and MRSA to establish and persist. The clinical consequences of this ecological shift are substantial: among individuals colonized with multidrug-resistant ESBL-producing bacteria, 22% progress to severe infections, including sepsis [25]. These mechanistic and clinical patterns illustrate how inappropriate antibiotic exposure at the patient level scales into broader ecological change, directly leading to the population-level burden of AMR observed across healthcare systems.

In the United States, 2.8 million antibiotic-resistant infections occur annually, resulting in more than 35,000 deaths [26]. Resistant infections increase hospitalization stays compared to their non-resistant counterparts, with multi-study cohorts reporting MRSA ICU stays averaged 5 days, while MSSA stays averaged 2 days. Additionally, resistant infections carried 26% higher rates of ICU admission and higher rates of mortality [27].

Resistant infections often require toxic or last-line agents such as polymyxins, which carry exceedingly high adverse event rates, including nephrotoxicity (30-60%), neurotoxicity (7-10%), and severe hypersensitivity reactions. These events correlate directly with mortality; in cases of CRE bacterial infections, mortality rates range from 30-50%, while MDR pneumonia ranges from 40-60% [28].

In the ED, biomarker-driven misclassification normalizes broad antibiotic use even when bacterial infection is unlikely, progressively reducing the effectiveness of standard therapies and increasing reliance on these high-risk agents. The downstream fueling of AMR creates a major global health hazard, underscoring the need for more accurate biomarkers to avoid unnecessary antibiotic use.

Clinical Implications in the ED: Workflow and Safety

The downstream consequences of misclassification are amplified by the operational realities of emergency care. Crowding, boarding, workflow fragmentation, and resource limitations create conditions in which early diagnostic uncertainty—driven by initial system failures—translate into triage distortion, misallocated resources, and safety-critical delays. These environmental pressures they intensify misclassification, shaping patient trajectories long before definitive diagnostic information becomes available.

Triage Distortion

Triage placement is one of the earliest points at which misclassification produces operational harm. Under-triage is common when bacterial sepsis is mislabeled as viral, often due to normal leukocyte count or low early PCT. These patients are subsequently placed in lower-acuity zones, monitored less frequently, and reassessed less often. Recent studies have demonstrated that early sepsis frequently goes unrecognized for hours after arrival, with clinical decision activation occurring a median of 3.5 hours post-presentation, reinforcing that misclassification at triage drives clinically meaningful delays [29,30]. Even when clinicians eventually identify sepsis presentation or phenotype, the initial misclassification has already produced delayed antibiotics and increased risk of deterioration, underscoring how biomarker-driven uncertainty at presentation cascades into direct operational harm, impacting patient care. These distortions destabilize ED flow and contribute to downstream resource strain, particularly during periods of high volume or limited staffing.

Resource Allocation and Throughput Failures

Emergency departments operate with finite telemetry monitors, resuscitation rooms, and nursing ratios. Misclassification indicating bacterial infections can trigger unnecessary fluid boluses, vasopressors, or invasive monitoring in viral illness, consuming high-acuity resources. Alternatively, misclassification toward viral illness can leave septic patients in low-acuity areas without telemetry, delaying recognition of hypotension or tachycardia [31].

Crowding magnifies these failures. A large AHRQ-commissioned systematic review found that diagnostic errors occur in 5.7% of ED encounters, with severe harm documented in 2.5 million cases annually [31], identifying crowding, time pressure, and chaotic clinical environments as major contributors to misdiagnosis. Each mis-triaged patient increases average ED length of stay by 1.2–2.4 hours [32], thus reducing bed availability for others and compounding throughput delays across the department.

Boarding further slows laboratory testing, imaging, and clinical reassessment, with boarded patients demonstrating higher likelihoods of errors in care [33,34]. Interruptions, multitasking, and rapid task switching increase cognitive burden and reduce diagnostic accuracy; workflow fragmentation accounts for 61.9% of preventable delay-related diagnostic errors [35]. Staffing shortages compress evaluation time, increasing reliance on heuristics and empiric therapy—conditions under which misclassification becomes more likely and more dangerous. This cascade self-reinforces, creating instability through ED workflows, and directly deteriorates the quality of care clinicians can provide.

Safety Events and Diagnostic Error Burden

The misclassification of bacterial sepsis toward viral illness—often driven by nonspecific early biomarkers—has been linked to patient safety events—specifically to premature discharge. Seventy-two-hour return admissions reveal substantial diagnostic failure; in one large ED cohort, 96% of investigated 72-hour revisits involved a diagnostic error, most arising from failures in the initial diagnostic pathway including incomplete assessment, missed deterioration, and failure to establish an adequate differential [36]. As crowding intensifies, safety events such as missed hypotension, delayed vital-sign reassessment, and unrecognized clinical decline become more likely, reflecting how operational strain magnifies the consequences of early diagnostic uncertainty and reduces opportunities for corrective reassessment.

Diagnostic errors represent the cumulative impact of these failures. They contribute to 7.4 million misdiagnosis and mistreatment events, linked to 350,000 morbidities in U.S. emergency care [37]. In sepsis, early diagnostic error accelerates physiologic deterioration; misdiagnosis can be deadly; each hour of delayed recognition increases mortality by 4–7% and is associated with worsening organ dysfunction [38].

Ultimately, unreliable early biomarkers initiate the misclassification cascade that drives safety events, diagnostic error, and preventable harm. Improving ED outcomes therefore requires diagnostic tools capable of resolving early uncertainty at its source rather than amplifying it across triage, workflow, and patient safety.

Conclusions

Early diagnostic uncertainty in emergency care is a structural consequence of relying on biomarkers that are biologically incapable of distinguishing bacterial from viral illness in the early hours of disease. CRP, PCT, lactate, and leukocyte count quantify downstream inflammatory byproducts, which have been statistically proven to lack diagnostic specificity. Their nonspecificity, delayed kinetics, and susceptibility to non-infectious confounders make early misclassification a predictable outcome rather than an exception.

This misclassification propagates through every layer of emergency care. It shapes early sepsis decisions, shifting life-saving antibiotics or antivirals outside their optimal therapeutic windows. Incorrect bacterial labeling delays life-saving antibiotics, while incorrect viral labeling promotes unnecessary antibiotic exposure, accelerates antimicrobial resistance, and increases the risk of adverse drug events. These clinical consequences accumulate rapidly during the narrow therapeutic window in which early sepsis care is most effective. At a population level, misclassification contributes to rising antimicrobial resistance, increased reliance on toxic last-line agents, and worsening treatment failures.

The operational realities of emergency care amplify this harm. Crowding, boarding, workflow fragmentation, and resource limitations create conditions in which early diagnostic uncertainty cascades into triage distortion, misallocated resources, premature discharge, and safety-critical delays. This operational strain directly magnifies diagnostic harm; mortality for time-sensitive conditions increases significantly during periods of ED crowding, creating an environment where early diagnostic uncertainty rapidly evolves into safety-critical delays and misallocated care. For acute care providers, these failures translate directly into preventable deterioration, ICU escalation, increased organ dysfunction, and sepsis.

This evidence demonstrates that current biomarkers do not meet the diagnostic demands of acute care for the differentiation of sepsis phenotype; rather, they propagate the harmful downstream consequences of misclassification in the ED. Traditional biomarkers fail at the precise moment when clinicians most need reliable physiologic guidance. Improving early sepsis outcomes therefore requires diagnostic tools capable of resolving uncertainty at the mechanistic level—tools that can differentiate bacterial from viral illness rapidly, accurately, and within the constraints of real-world ED workflow. Without such advances, misclassification will remain embedded in emergency care, perpetuating avoidable harm for patients and compounding strain on clinicians and health systems.

Future Directions

Improving early sepsis diagnosis requires tools capable of

resolving the mechanistic uncertainty that current biomarkers cannot address. CRP, PCT, lactate, and leukocyte count quantify downstream inflammatory injury rather than the upstream immune programs that differentiate bacterial from viral illness. If emergency clinicians continue to rely on these late-stage, nonspecific signals, early misclassification will remain a hallmark of acute care. Future diagnostic innovation must therefore focus on capturing upstream trajectories, rather than its downstream consequences as traditional biomarkers do.

One priority is the development of rapid assays that measure early immune activation patterns with sufficient granularity to distinguish infectious phenotypes at first contact. Technologies capable of detecting upstream host signatures—such as pathogen-agnostic immune response profiles, specific early cytokine or chemokine patterns, or cellular activation states—may provide actionable information within the narrow therapeutic window in which early sepsis care is most effective. These approaches must be designed for ED realities: turnaround times measured in minutes, minimal sample processing, and resilience to confounders such as trauma, chronic inflammation, or comorbid disease.

Equally important is integrating diagnostic tools into ED workflow in ways that reduce cognitive load rather than add to it. Decision support systems that synthesize early immune signals with vital signs, comorbidities, and risk scores could help clinicians anchor diagnostic reasoning more accurately under conditions of crowding, interruptions, and incomplete data. Such systems must be transparent, interpretable, and aligned with clinical intuition to avoid contributing to alert fatigue or workflow fragmentation.

Finally, future research should evaluate how improved early diagnostics influence downstream outcomes across the entire sepsis pathway. Studies should examine not only mortality and antibiotic timing, but also stewardship performance, AMR trends, triage accuracy, resource allocation, and diagnostic error rates. Understanding how early diagnostic certainty propagates through ED operations will be essential for designing tools that meaningfully reduce misclassification and improve patient safety.

These directions point to a diagnostic paradigm that moves beyond late-stage inflammatory biomarkers and toward mechanistic, rapid, and workflow-compatible tools. At this level, resolving the diagnostic uncertainties traditional biomarkers create becomes a clinical and operational imperative for improving sepsis care in the emergency department.

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