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POINT OF VIEW
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Circulatory biomarkers for microbial infections

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ABSTRACT

This article explores the paradigm shift in infectious disease diagnostics from direct pathogen detection to host-response profiling. While traditional markers like C-reactive protein (CRP) and procalcitonin (PCT) are clinical staples, they lack the specificity required for precision antimicrobial stewardship. The perspective highlights the emergence of presepsin as a superior early-phase bacterial biomarker and the development of multi-parametric mRNA signatures that differentiate viral from bacterial etiologies with high sensitivity. Furthermore, the expansion into pan-microbial surveillance, incorporating fungal (BDG, Galactomannan) and protozoal (HRP2/pLDH) markers, addresses critical blind spots in empiric therapy. Despite challenges regarding cost and standardization, the integration of these circulatory biomarkers with AI-driven decision support is poised to slowly replace empiric treatment with precision stewardship. This transition enables the triangulation of infection etiology within the clinical "golden hour", ultimately improving patient outcomes and combating antibiotic resistance.

Keywords: Host-response profiling, Precision diagnostics, Pan-microbial surveillance

The transition from pathogen detection to host-response profiling represents the decisive paradigm shift in modern infectious disease diagnostics. While traditional biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) remain clinical staples, the integration of novel molecules like presepsin and multi-parametric mRNA signatures is finally enabling the differentiation of viral versus bacterial etiology with the precision required for effective antimicrobial stewardship.

The silent signal: decoding the host response

The clinical void

For decades, the "gold standard" of blood culture has been a slow standard, often requiring 24-72 hours to yield actionable data. In the interim, clinicians operate in a diagnostic vacuum, driving the empiric overuse of broad-spectrum antibiotics. The immediate physiological response to infection—the "circulatory whisper" of the host immune system—offers a faster alternative. However, the ideal biomarker must thread the needle between sensitivity (catching the infection early) and specificity (ignoring non-infectious inflammation like trauma or surgery).

The incumbents: CRP and procalcitonin

C-reactive protein (CRP) and procalcitonin (PCT) define the current standard of care. CRP, while highly sensitive, is the blunt instrument of inflammation, rising indiscriminately in response to autoimmune flares, tissue injury, and infection. PCT offers an upgrade, demonstrating higher specificity for bacterial etiologies and correlating with bacterial load. However, recent meta-analyses from 2025 highlight significant limitations: PCT levels can be confounded by renal impairment and non-infectious systemic stress, leading to false alarms in critical care settings. The need for a marker that reflects the severity of the infection rather than just the presence of inflammation is paramount. The next generation of biomarkers moves beyond simple inflammation to track specific immune pathway activation.

Presepsin

Presepsin (soluble CD14 subtype) has emerged as a noteworthy competitor to PCT. Unlike PCT, which is a precursor protein, presepsin is released directly by monocytes/macrophages upon phagocytosis of bacteria. Recent data indicate presepsin may offer superior diagnostic accuracy in the early phases of sepsis (1, 2). Presepsin peaks as early as 2 hours post-infection—significantly faster than PCT—and correlates more strongly with sequential organ failure assessment (SOFA) scores and 28-day mortality risk. Furthermore, presepsin appears less influenced by non-infectious inflammation, potentially offering a clearer signal in complex trauma patients.

The omics revolution: viral vs. bacterial

The most profound advancement lies in differentiating bacterial from viral infections—the "Holy Grail" of antibiotic stewardship. New assays, such as the MeMed BV®, utilize a computational algorithm combining three host proteins (TRAIL, IP-10, and CRP) to distinguish viral from bacterial

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responses with over 90% sensitivity (3). Simultaneously, host-gene expression classifiers (mRNA signatures) are moving from the bench to the bedside. By analyzing the upregulation of specific genomic pathways (e.g., interferon signaling for viruses vs. antibacterial effector genes), these tools can identify bacterial infections even when cultures remain negative.

Fungal and protozoal infections

The expansion of the diagnostic lens from a bacterial-viral binary to a pan-microbial perspective represents the critical next step in sepsis management. While presepsin and mRNA signatures are revolutionizing bacterial differentiation, the integration of biomarkers for invasive fungal infections (IFI) and protozoal sepsis (e.g. malaria) is essential for closing the blind spots in empiric therapy (Table 1). Invasive fungal infections remain a lethal blind spot in critical care, often identified only after broad-spectrum antibiotics fail. The shift is towards non-culture surveillance.

1,3-β-D-Glucan (BDG): It acts as a pan-fungal smoke detector. It detects a cell wall component common to *Candida*, *Aspergillus*, and *Pneumocystis*. While its sensitivity allows it to detect infection days before clinical symptoms, its specificity is its Achilles' heel—hemodialysis filters and certain antibiotics can trigger false alarms (4).

Galactomannan (GM): It offers higher specificity for invasive Aspergillosis, particularly in neutropenic patients. Unlike BDG, GM is released during active hyphal growth, making it a proxy for fungal load. The combination of BDG (for screening) and GM (for confirmation) is becoming the gold standard for ruling out fungal sepsis in the immunocompromised.

The parasitic signal: malaria and leishmania

For protozoal infections, the biomarker landscape is dominated by the need for speed in low-resource settings.

Malaria (The HRP2/pLDH Dichotomy): The diagnosis of *Plasmodium falciparum* relies heavily on histidine-rich protein 2 (HRP2). It is abundant and heat-stable, making it ideal for rapid diagnostic tests (RDTs). However, HRP2 persists in the blood for weeks after the parasite is cleared, making it irrelevant for monitoring "cure". Plasmodium lactate dehydrogenase (pLDH) is produced only by live parasites. pLDH levels crash immediately upon effective treatment, serving as a real-time biomarker for therapeutic efficacy (5).

Leishmaniasis: While less developed than malaria diagnostics, biomarkers for Visceral Leishmaniasis are moving toward host-response signatures. Elevated IL-10 and vascular endothelial growth factor (VEGF) have been identified as markers of acute disease activity, with their normalization signaling treatment success, potentially replacing invasive splenic aspirates.

Conclusion

Despite the scientific promise, the translation of these biomarkers into routine clinical practice faces logistical hurdles. The cost of novel assays, the need for rapid turnaround times (<1 hour), and the lack of standardized cut-off values for diverse populations (e.g., neonates vs. geriatrics) remain significant barriers. The future of infectious disease management is not only in finding the bug, but also in understanding the host response. The shift from single-molecule detection to multi-parametric algorithmic scoring represents the maturity of the field. As we move toward 2030, the integration of these circulatory biomarkers with AI-driven clinical decision support systems will likely retire the concept of empiric therapy, replacing it with precision stewardship. The future approach may rely more on probabilistic algorithms than on any single biomarker. By combining fast-response bacterial markers (presepsin) with high-NPV (negative predictive value) viral scores (TRAIL: TNF-related apoptosis-induced ligand) and specific fungal/parasitic antigens, we can triangulate the etiology of shock within the "Golden Hour".

It should be noted that the use of circulating biomarkers is not always recommended as a standalone diagnostic tool for every case of suspected microbial infection. Instead, their utility is highly context-dependent. They are most valuable when "speed" is critical or when "clinical ambiguity" is high, rather than as a routine replacement for traditional culture-based microbiology methods in all scenarios. Use of biomarkers may be favored when there is a need to make an immediate decision (medical emergency), or the clinician is unsure whether a fever is bacterial or viral, or culture facilities are not available. It is advisable not to rely solely on biomarkers in cases like a clear localized infection (e.g., skin abscess), the patient has a condition that skews results (e.g., recent major surgery), or one needs to know which antibiotic to use (which requires culture sensitivity) (6). Even after emergency use of biomarker-based assays, subsequent pathogen identification remains critically relevant and is often the indispensable "second half" of the diagnostic process. While circulating biomarkers excel at answering questions like: is there an infection? When should we start/stop

TABLE 1 - Potential biomarkers for various microbial infections

Pathogen Class	Key Biomarker	Kinetic Profile	Clinical Utility & Limitations
Bacterial	Presepsin	Peaks ~2h post-infection (Rapid)	Superior early sensitivity; differentiates sepsis from non-infectious SIRS.
Fungal	1,3-β-D-Glucan (BDG)	Elevated days/weeks pre-symptoms	Pan-fungal surveillance (Candida/Aspergillus); prone to false positives (dialysis, antibiotics).
Protozoal	HRP2/pLDH	Persistent (HRP2) vs. Reactive (pLDH)	HRP2 confirms *P. falciparum*; pLDH tracks treatment success as it clears rapidly.
Viral	TRAIL/IP-10	Interferon-driven response	High negative predictive value for bacterial use; reduces unnecessary antibiotics.

the treatment? They often fail to provide any clue regarding which specific organism has caused the infection and which antibiotic may prove most effective. Biomarkers and pathogen identification approaches should be viewed as complementary partners, not competitors. While biomarkers buy us time and confidence to act quickly, accurate pathogen identification ensures that therapeutic action is correct and sustainable.

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