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Editorial

Sepsis Biomarkers: A Mandate Point-of-Care Tests for Every ICU in India

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INTRODUCTION

Sepsis is a leading cause of mortality in ICUs in India, using high resources. Despite the major advancements in critical care, case-fatality rates remain high because of delayed recognition, usage of empiric broad-spectrum antibiotics, and a high burden of multiple drug-resistant organisms (MDROs) [1, 4]. The cost of antimicrobial resistance (AMR) in Indian ICUs is substantial due to longer hospital stays, expensive last resort drugs, organ support, and excess mortality, imposing a heavy financial and societal toll [4]. Diagnostic uncertainty amplifies the problem when clinicians can't rapidly distinguish bacterial from fungal causes of sepsis, or sepsis from sterile inflammation, leading them to default to "cover all causative agents," which accelerates AMR and adverse events. The Indian experience highlights how diagnostic errors cascade into incorrect antimicrobial choices and worse outcomes, strengthening the case for diagnostic stewardship as the front end of antimicrobial stewardship (AMS) [5].

Recognizing this, the Society of Antimicrobial Stewardship PractIces (SASPI) in India has issued a list of Integrated Antimicrobial Stewardship (IAS) practice statements highlighting rapid diagnostics as a pillar of AMS implementation at the bedside. Point-of-care (POC) sepsis biomarkers are now a pragmatic, scalable, adaptable, and dynamic driver to reduce time-to-targeted therapy, shorten antimicrobial exposure, and curb AMR for Indian ICUs both public and private, large and small [6, 7].

WHAT ARE SEPSIS BIOMARKERS AND HOW DO THEY HELP?

Bacterial sepsis marker: Procalcitonin (PCT)

PCT rises with systemic bacterial infection and falls as infection resolves. Although it is not a specific marker for sepsis, its serial trends help us determine when to de-escalate or stop antimicrobials. Randomized and economic evidence shows that fewer antimicrobial days and better cost-effectiveness were observed when PCT guides antibiotic stopping rules in ICU patients [8, 9].

Fungal sepsis markers: Galactomannan (GM) & 1,3-β-D-glucan (BDG)

GM is one of the cell wall components of *Aspergillus spp.* and reflects Aspergillus antigenemia, whereas BDG signals a broad range of invasive fungal infections (IFIs). In Indian ICUs, where invasive candidiasis and aspergillosis are increasingly recognized, these non-culture-based fungal assays enable earlier rule-in/rule-out, replacing weeks of empirical antifungals or antibiotics with care driven by diagnostics [3, 10, 12]. UK real-world analyses show GM/BDG-anchored pathways lower antifungal/antibiotic exposure, length of therapy, and total costs while maintaining or improving outcomes [11, 12].

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Old & emerging markers

In the field of evolution, many biomarkers have been adopted by the POC diagnostic division. They also provide robustness and depth to sepsis diagnosis and monitoring within these complex patient cohorts, including their principles that are clinically acceptable and evidence-based (Box 1).

Box 1: Details of major sepsis biomarkers

Biomarker	Lab Principle	Typical TAT	Sensitivity / Specificity*	Remarks
Procalcitonin (PCT)	Immunoassay (chemiluminescent / turbidimetric)	1–2 h	75–90% / 70–85%	Best for antibiotic stopping rules and trend-based de-escalation; anchor of bacterial diagnostic stewardship [8, 9].
Galactomannan (GM)	ELISA on serum/BAL	4–6 h	70–90% / 80–90%	Supports aspergillosis dx; broncho-alveolar lavage GM > serum for ICU; use with host/radiology and pretest probability [10, 11].
β-D-Glucan (BDG)	Colorimetric/ turbidimetric	4–6 h	65–85% / 75–90%	Broad invasive fungal infections screen (Candida, Aspergillus, Pneumocystis); negative BDG helps stop empiric antifungals [11, 12].
C-reactive protein (CRP)	Immunoturbidimetry	1–2 h	60–70% / 50–70%	Non-specific; supportive when combined with PCT/clinical scores; don't use alone for ICU decisions [8].
Interleukin-6 (IL-6)	Immunoassay	2–4 h	70–80% / 65–75% (variable)	Early inflammatory signal; adjunct to PCT/sequential organ failure score for triage and prognosis evaluation; mixed stand-alone accuracy [13].
Presepsin (sCD14-ST)	Chemiluminescent immunoassay	2–3 h	75–85% / 70–80% (heterogeneous)	Emerging adjunct; heterogeneity & access limit routine ICU use; consider in research/selected settings [14].

*Performance ranges approximate pooled ICU data pertaining adult patients and vary by threshold, timing, and population [8, 14].

- C-reactive protein (CRP) testing is widely available and inexpensive, but the specificity for sepsis is modest and should not be used alone to start/stop antimicrobials [8]. Interleukin-6 (IL-6) is an inflammatory cytokine that rises early and rapidly. When used as a single test, its diagnostic accuracy is variable, but it can augment early risk assessment or bundled triage when paired with PCT and clinical parameters [13]. Presepsin (sCD14-ST) shows promise in meta-analyses, but the heterogeneity and the access to testing assay limit its routine use in the ICU. It may be considered as an adjunctive rather than an essential marker, currently [14].
- Serum lactate is indispensable for diagnosing sepsis severity and monitoring organ dysfunction due to anaerobic causative agents of sepsis, as it is a very well-validated measure of anaerobic metabolism and tissue hypoperfusion [15].
- Total leukocyte count (TLC), though non-specific, it remains a basic yet crucial indicator of acute host response and disease progression in resource-limited settings.
- Emerging markers such as CD64, a neutrophil activation marker, and sTREM-1 (soluble triggering receptor expressed on myeloid cells) have shown improved sensitivity and early

detection capability for differentiating sepsis from other inflammatory conditions. Their utility, although promising, still requires broader validation in diverse populations [16].

- Cryptococcal antigen (CrAg) detection primarily from the CSF samples is rapid, sensitive, and increasingly implemented in Indian clinical practice, which is particularly useful for diagnosing cryptococcal meningitis, especially among immunocompromised patients.
- Candida Mannan/Anti-Mannan assays help clinicians by giving an early diagnostic advantage as the turnaround time is less, when combined with BDG or GM, improving sensitivity and specificity for diagnosing invasive candidiasis.
- Histoplasma antigen is a highly sensitive marker, for disseminated histoplasmosis, particularly in immunocompromised or critically ill patients. Its rapid turnaround time and easy detection in urine samples make it a valuable adjunct in the early evaluation of fungal sepsis. When used alongside other biomarkers such as PCT, GM, BDG, CrAg, and mannan assays, Histoplasma antigen testing enhances diagnostic accuracy, ruling out other causes and facilitating timely, targeted antifungal therapy for histoplasmosis [17].

WHY EVERY ICU IN INDIA SHOULD OPERATIONALIZE BIOMARKER-GUIDED CARE NOW?

1) ***Mortality and morbidity reductions through faster, targeted treatment***
By differentiating bacterial vs fungal vs inflammatory syndromes early, biomarker bundles will shorten time-to-appropriate therapy and reduce inappropriate coverage, which is critical in settings with rising carbapenem-resistant Gram-negatives organisms and IFIs [2-4, 10]. PCT-guided protocols consistently reduce antibiotic days, signaling towards improved survival in pooled ICU data [9]. GM/BDG-driven pathways curb unnecessary antifungals while protecting high-risk patients from any delays in therapy [11, 12].

2) ***Antimicrobial savings & AMR containment***
India's AMR burden is among the world's highest, with substantial excess costs at ICU-level [2-4]. Every day avoided of broad-spectrum exposure reduces selection pressure and downstream the harm caused by *Clostridioides difficile* and *Candida spp.* PCT algorithms trim the antibiotic duration without increasing failures [8, 9]. Diagnostic-driven fungal strategies avoid empiric azoles/echinocandins unless indicated [11, 12].

3) ***Shorter ICU/hospital stays and lower costs***
AMR cases in Indian ICUs add significant incremental cost and length of stay (LOS) [4]. When biomarker-guided care de-escalates therapy and speeds definitive treatment, LOS and drug spend drop, which is a double dividend for patients and payers. UK economic studies for fungal diagnostics show per-patient savings. With this, Indian ICUs can realize similar directional benefits by integrating GM/BDG with stewardship oversight [11, 12].

4) ***Fits national priorities & Indian stewardship practices***
ICMR surveillance confirms the AMR headwinds confronting hospitals, while the SASPI IAS practice statements enumerate 42 practice points, including early diagnostic stewardship and rapid tests as a backbone of AMS in Indian hospitals [3, 6, 7]. A combination of tests detecting PCT with GM or BDG at triage and day-2 reviews directly operationalizes those points in the ICU workflow.

IMPLEMENTATION IN INDIAN ICU

A three-test essential panel can be launched in each ICU, which includes PCT for bacterial sepsis and GM and BDG for suspected IFI (e.g., pyrexia of unknown origin on broad-spectrum antibiotics, hosts exposed to filamentous fungi, influenza/COVID-19).

Start with a four-step protocol in each ICU:

Step 1: Initial Assessment (Day 0)
On clinical suspicion of sepsis, baseline PCT, blood cultures, and appropriate imaging need to be done. Start empiric antibiotics ± antifungals as per existing ICU protocol. In high-risk or immunocompromised patients with history of persistent fever, send samples for investigating the presence of IFIs with the markers like GM and BDG.

Step 2: Reassessment at 24–48 Hours
- If PCT decreases by ≥80% from peak or ≤0.5 ng/mL, and/or blood cultures are negative, consider stopping or narrowing antibiotics [8, 9].
- If PCT remains high or rising, review source control, culture results, and escalate only if clinically indicated.
- For suspected IFIs, negative GM or BDG results support withholding antifungals whereas positive tests justify early targeted antifungal therapy [10, 11].

Step 3: Ongoing Monitoring (Day 3–5)
Repeat PCT every 48 hours if antibiotics are continued. Persistent reduction of its values supports right treatment/de-escalation and lack of fall will signal unresolved infection or complication.

Step 4: Stop rule Exclusions

Clinical presentations like infective endocarditis, osteomyelitis, deep-seated abscesses, prosthetic infections, or CNS sepsis need to be excluded as specific guidelines are followed with respect to duration too. Stop rules cannot be applied in these conditions [9].

This structured pathway integrates biomarkers into daily ICU decision-making, ensuring antibiotics and antifungals are administered only as long as clinically necessary and reducing resistance, costs, and toxicity.

Training & governance

Use the SASPI IAS checklist and local antibiogram-GM/BDG pathways; AMS+ICU co-lead the daily 'diagnostics & de-escalation' huddle. Quality indicators include antimicrobial days of therapy (DOT), time-to-active therapy, antifungal days, length of stay (LOS), and ICU mortality [6, 7].

Back-of-the-envelope business case (100 hospitals/year)

- Sepsis admissions per ICU/year: 1,000
- Antibiotic days reduced with PCT algorithms: −1.5 to −3.0 days per patient [8, 9]
- Empiric antifungal courses avoided/shortened by GM/BDG: 10–20% of suspected IFI episodes [11, 12]
- ICU bed-day & antifungal/antibiotic costs: local finance data vary; directionally, fewer days and drugs = lower spend [4, 11, 12]

If each ICU avoids 2 antimicrobial days per patient and prevents/shortens antifungal therapy in 15% of suspected IFI episodes, a 100-ICU cohort (≈100,000 sepsis admissions/year) can avert ≈200,000 antimicrobial days and thousands of antifungal days, translating into large drug and bed-day savings and fewer AMR complications, without harm to patients. Even after reagent/analyzer costs, RCT and modelling data suggest net savings with PCT-guided care and cost reductions with diagnostic-driven fungal strategies [9, 11, 12]. Over 5 years, expanding by 100 hospitals/year builds national coverage while standardizing practice around SASPI-aligned diagnostics. More importantly, each ICU can progressively adopt all evidence-based sepsis biomarkers as described previously, including metagenomics.

Limitations

These biomarkers are internationally recognized POC tests for sepsis, but their performance in Indian ICUs can be compromised by several unique epidemiological and clinical variables. High rates of concurrent bacterial, viral, parasitic, and fungal infections can confound biomarker readings, dampening specificity and leading to false positives or negatives, especially with GM and BDG in patients exposed to environmental fungi or receiving certain antibiotics [18]. Most of the ICU patients are malnourished, which alters immune responses and may attenuate or exaggerate biomarker responses. There is a high suspicion that BDG and GM levels may be lower in malnourished hosts due to reduced fungal burden or altered metabolism. According to Indian epidemiology of infectious diseases where dengue and tuberculosis are highly endemic, the cytokine storm in these diseases can profoundly influence the reliability of PCT, forcing clinicians to critically re-evaluate the diagnostic cut-offs traditionally used in Western cohorts.

CONCLUSION

The ICUs in Indian hospitals face a dual crisis of the rapid rise of AMR and lethal outcomes of sepsis, leaving no options for treating the deadly infections. The fastest path to safer, cheaper, and smarter care is with diagnostic stewardship by including testing for biomarkers of sepsis, like PCT, to correctly guide the usage of antibiotics and GM and BDG to target antifungals, which should be further supported by culture, imaging, and clinical parameters. The current scenario in our country, including biomarker testing, is like a luxury, but it should become a foundational AMS infrastructure, as already reflected in national surveillance priorities and SASPI's IAS practice statements. A disciplined, measured roll out of approximately 100 hospitals each year will reduce mortality, costs incurred, and protect antimicrobial efficacy for the next generation. The question for every ICU should no longer be "Should we implement biomarker-guided sepsis care?" but "How fast can we implement biomarker-guided sepsis care?"

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