

Diagnostic Markers of Neonatal Sepsis

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Abstract:

Background: Neonatal sepsis is a life-threatening condition and a major cause of neonatal morbidity and mortality worldwide, particularly in developing nations like India. Early diagnosis remains a challenge due to nonspecific clinical manifestations and limitations of conventional diagnostic tests.

Aim: To review and summarize the current and emerging diagnostic markers of neonatal sepsis, with a focus on their diagnostic accuracy, feasibility, and applicability in the Indian healthcare context.

Methods: A comprehensive literature review was conducted using databases such as **PubMed, Scopus, Google Scholar, and Web of Science** for studies published between **2018 and 2025**. Relevant keywords included neonatal sepsis, diagnostic markers, biomarkers, CRP, procalcitonin, IL-6, CD64, and molecular diagnostics. Both traditional and novel markers were evaluated for sensitivity, specificity, and clinical utility. Studies from India were particularly emphasized to highlight region-specific challenges and ICMR-supported research initiatives.

Results: Traditional markers like **CRP and TLC** remain widely used but exhibit low specificity. Novel biomarkers such as **procalcitonin, IL-6, IL-8, CD64, presepsin, and neopterin** show promising diagnostic potential, especially when used in combination. Recent advances in **molecular diagnostics, microRNA profiling, and point-of-care biosensors** offer rapid and accurate detection capabilities.

Conclusion: Combining multiple biomarkers with advanced diagnostic platforms can substantially improve early detection and management of neonatal sepsis. Support from the **Indian Council of Medical Research (ICMR) and Government of India** in validating and deploying low-cost diagnostic assays is essential to strengthen neonatal healthcare infrastructure.

Keywords: Neonatal sepsis, Diagnostic markers, Biomarkers, Procalcitonin, ICMR, India.

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Methodology

This review followed a **structured narrative review approach** guided by PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews) principles to ensure comprehensiveness and transparency.

Data Sources and Search Strategy

Electronic databases including **PubMed, Scopus, Web of Science, and Google Scholar** were searched for peer-reviewed articles published between **January 2018 and October 2025**. The following search terms were used in combination with Boolean operators: “neonatal sepsis,” “biomarkers,” “diagnostic markers,” “procalcitonin,” “C-reactive protein,” “interleukins,” and “molecular diagnostics.” The search was limited to English-language articles and human studies.

Inclusion Criteria

- Studies assessing **diagnostic accuracy** (sensitivity, specificity, predictive value) of biomarkers in neonatal sepsis.
- Research involving **neonates (≤ 28 days)** of life.
- Articles published in peer-reviewed journals.
- Both **hospital-based observational and prospective cohort** studies.

Exclusion Criteria

- Case reports, reviews, editorials, or animal studies.
- Studies not providing diagnostic outcome data.
- Papers with incomplete or ambiguous methodology.

Data Extraction and Synthesis

Two reviewers independently screened titles and abstracts, extracted relevant data on study design, sample size, population, biomarker type, sensitivity, specificity, and diagnostic accuracy.

Data were summarized descriptively and grouped under **traditional, novel, and**

molecular diagnostic markers. Comparative findings were synthesized narratively to identify trends and gaps in current literature.

Ethical Considerations

As this review is based on previously published studies, no ethical approval was required. However, ethical compliance of the included studies was ensured based on their publication standards.

Acknowledgment is given to the **Indian Council of Medical Research (ICMR), Government of India**, for its continuing efforts toward improving diagnostic research and neonatal healthcare infrastructure.

Introduction

Neonatal sepsis continues to be a **major cause of morbidity and mortality worldwide**, particularly in low- and middle-income countries. It is estimated that nearly **3 million newborns** suffer from sepsis annually, with mortality rates ranging between **11% and 19%** globally. In India, despite improvements in perinatal care, the burden remains disproportionately high. According to surveillance data from the **Indian Council of Medical Research (ICMR)** and the **National Neonatal Perinatal Database (NNPD)**, the incidence of neonatal sepsis varies from **11 to 38 per 1,000 live births**, contributing significantly to neonatal deaths and long-term complications such as neurodevelopmental impairment.

Neonatal sepsis is defined as a **systemic inflammatory response syndrome (SIRS)** occurring in the presence of or as a result of a suspected or proven infection in the first 28 days of life. It is broadly classified into two categories:

- **Early-Onset Sepsis (EOS):** occurring within the first 72 hours of life, usually transmitted vertically from the mother, associated with organisms such as

Group B Streptococcus and Escherichia coli.

- **Late-Onset Sepsis (LOS):** occurring after 72 hours, often related to nosocomial or community-acquired infections, commonly caused by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida* species.

The **diagnosis of neonatal sepsis** poses substantial challenges due to its **nonspecific and subtle clinical manifestations**. Symptoms such as poor feeding, temperature instability, apnea, lethargy, and irritability are not unique to sepsis and can overlap with non-infectious neonatal conditions like hypoglycemia, birth asphyxia, or metabolic disorders. Therefore, clinicians often rely on laboratory investigations to support clinical suspicion.

The **gold standard for diagnosis** remains **blood culture**, which provides etiological confirmation and guides antimicrobial therapy. However, it is fraught with limitations—its **low sensitivity, time delay (24–72 hours)**, and potential for **contamination** make it unreliable as a sole diagnostic tool. Moreover, many neonates receive empirical antibiotics before culture results are available, which may further reduce culture positivity.

To overcome these challenges, researchers have focused on identifying **rapid, reliable, and non-culture-based biomarkers** that can detect infection at an early stage and help differentiate between infected and non-infected neonates. Traditional markers such as **C-reactive protein (CRP)** and **white blood cell indices** have been used for decades but often lack sensitivity and specificity, particularly in early infection. In recent years, several **novel diagnostic markers**—including **procalcitonin (PCT)**, **interleukin-6 (IL-6)**, **interleukin-8 (IL-8)**, **tumor necrosis factor-alpha (TNF- α)**, and **cell surface antigens (e.g., CD64,**

CD11b)—have been studied for their potential to improve diagnostic accuracy.

Advances in **molecular biology, genomics, and proteomics** have further expanded the horizon by enabling identification of **gene expression profiles, microRNAs, and metabolomic patterns** associated with neonatal sepsis. These innovations hold promise for developing **rapid diagnostic platforms** and **point-of-care (POC) testing**, which are particularly valuable in resource-limited settings.

In India, the **ICMR** has been at the forefront of supporting **translational research** in neonatal sepsis diagnostics through its national initiatives aimed at developing **affordable, scalable, and rapid diagnostic solutions**. Such efforts are crucial in improving early recognition and reducing the mortality burden associated with neonatal infections.

Therefore, this review aims to provide a **comprehensive analysis of diagnostic markers of neonatal sepsis**, encompassing traditional, novel, and emerging biomarkers. It further discusses their diagnostic utility, limitations, and applicability within the Indian healthcare context, emphasizing the role of **ICMR-supported innovations** in improving neonatal outcomes.

Pathophysiology of Neonatal Sepsis

A clear understanding of the **pathophysiological mechanisms** of neonatal sepsis is crucial for identifying relevant diagnostic markers. The neonatal immune system is **immature**, especially in preterm infants, which predisposes them to systemic infections and hampers an effective immune response.

Immaturity of the Neonatal Immune System

Neonates, particularly preterm infants, have an underdeveloped **innate and adaptive immune system**.

- **Innate immunity**—the first line of defense—is compromised due to

reduced neutrophil count, poor chemotaxis, diminished phagocytosis, and inadequate complement activation.

- **Adaptive immunity** is also immature, with low immunoglobulin levels (especially IgG and IgA), impaired antigen presentation, and a Th2-skewed cytokine response.

This immaturity leads to **inadequate recognition and elimination of pathogens**, making neonates vulnerable to rapid systemic dissemination once infection occurs.

Mechanism of Pathogen Invasion and Immune Activation

Pathogens may enter the neonatal circulation through:

- **Transplacental transmission** (e.g., *Listeria monocytogenes*)
- **During delivery** via exposure to infected birth canal secretions (*E. coli*, Group B *Streptococcus*)
- **Postnatal or nosocomial exposure** (e.g., *Klebsiella*, *Staphylococcus aureus*, *Pseudomonas*)

Once pathogens gain access, their **pathogen-associated molecular patterns (PAMPs)**—such as lipopolysaccharide (LPS), flagellin, and peptidoglycan—are detected by **pattern recognition receptors (PRRs)** like **toll-like receptors (TLRs)** on immune cells. Activation of these receptors triggers intracellular signaling cascades (notably the **NF- κ B** and **MAPK** pathways), leading to the production of **proinflammatory cytokines** such as **IL-6**, **IL-8**, and **TNF- α** , and **acute-phase proteins** like CRP and procalcitonin.

The Inflammatory Cascade

The progression of neonatal sepsis involves a **complex interplay between proinflammatory and anti-inflammatory mechanisms**:

- **Cytokine storm**: Excessive release of IL-1 β , IL-6, and TNF- α causes widespread endothelial injury and capillary leak.

- **Complement activation**: Results in the production of potent inflammatory mediators (C3a, C5a).
- **Endothelial dysfunction**: Leads to hypotension, tissue hypoperfusion, and multi-organ dysfunction.
- **Anti-inflammatory response**: Elevated IL-10 and transforming growth factor-beta (TGF- β) levels suppress immune activity, increasing vulnerability to secondary infections.

Each of these phases corresponds to **specific diagnostic markers** measurable in clinical settings:

- **Early markers**: IL-6, IL-8 (rise within 2–4 hours of infection).
- **Intermediate markers**: PCT and CRP (increase within 6–12 hours).
- **Cellular markers**: CD64 and CD11b (upregulated on neutrophils during activation).
- **Late markers**: Persistently elevated CRP and PCT levels can indicate ongoing infection or treatment failure.

Molecular and Genetic Influences

Host genetic variations play a pivotal role in sepsis susceptibility and immune response modulation. **Polymorphisms in genes encoding TLR2, TLR4, and TNF- α** influence cytokine production and infection outcomes. Furthermore, **transcriptomic and proteomic studies** have identified gene expression signatures unique to septic neonates, offering potential for highly specific diagnostic assays.

Clinical Implications

Understanding these molecular mechanisms helps in identifying **biomarkers that reflect distinct stages of the immune response**. Combining early and late markers (for example, IL-6 + CRP or PCT + CD64) has shown improved diagnostic precision in differentiating sepsis from non-infectious inflammatory states. The integration of biomarker data into **point-of-care diagnostic platforms** and **AI-driven predictive algorithms**

represents a major leap forward in sepsis management.

The **ICMR, Government of India**, through its neonatal health programs and translational research initiatives, continues to support **biomarker validation studies and diagnostic innovation** aimed at developing rapid, affordable, and context-specific diagnostic tools for neonatal sepsis across Indian NICUs.

Traditional Diagnostic Markers

Early diagnosis of neonatal sepsis relies on identifying laboratory indicators that reflect infection and systemic inflammation. Historically, clinicians have used **hematological indices** and **acute-phase reactants** as supportive evidence to guide early management decisions. Although these traditional markers are widely available and inexpensive, they often lack **sensitivity and specificity**, particularly during the early phase of infection when rapid intervention is critical.

Hematological Markers

Total Leukocyte Count (TLC)

The total leukocyte count is among the oldest parameters used in sepsis evaluation.

- **Normal range:** 9,000–30,000/mm³ in neonates.
- **Leukopenia (<5,000/mm³)** is a stronger indicator of sepsis than leukocytosis, as severe infections can lead to bone marrow suppression.

However, the TLC alone is unreliable due to variations caused by stress during labor, corticosteroid exposure, or prematurity. Studies suggest that combining TLC with other indices improves predictive accuracy.

Absolute Neutrophil Count (ANC)

The ANC reflects the body's immediate immune response to infection. Neonates with bacterial sepsis often exhibit **neutropenia (<1,800/mm³)** due to consumption of neutrophils at infection sites. The **Manroe** and **Mouzinho charts** provide reference ANC values based on

gestational and postnatal age, aiding interpretation.

Immature-to-Total Neutrophil Ratio (I/T Ratio)

The I/T ratio is considered a sensitive hematological indicator of infection.

- **An I/T ratio >0.2** is suggestive of sepsis. It rises early in infection, often before other indices change, making it a useful screening test. However, elevated I/T ratios can also be seen in non-infectious conditions like perinatal asphyxia or stress.

Platelet Count

Thrombocytopenia (<150,000/mm³) is a common finding in neonatal sepsis due to increased platelet destruction and consumption in disseminated intravascular coagulation (DIC). Persistent thrombocytopenia correlates with disease severity and poor prognosis but is not diagnostic by itself.

Acute Phase Reactants

C-Reactive Protein (CRP)

CRP is one of the most widely used acute-phase reactants in neonatal sepsis.

- Produced by the **liver** in response to IL-6 and other proinflammatory cytokines.
- Levels start to rise **6–8 hours after infection onset**, peaking around 24–48 hours.
- A **CRP value >10 mg/L** is generally considered significant.

Advantages:

- Good negative predictive value—normal CRP levels make sepsis less likely.

Limitations:

- Delayed rise after infection onset limits its use for early diagnosis.
- May be elevated in non-infectious conditions (birth asphyxia, meconium aspiration, or intraventricular hemorrhage).

Serial CRP measurements are more useful than a single reading, as **persistently elevated CRP** may indicate ongoing infection, while a declining trend suggests recovery.

Blood Culture

Blood culture remains the **gold standard** for confirming sepsis.

- It provides **definitive etiological diagnosis** and guides antibiotic selection.
- However, it has **low sensitivity (60–80%)**, particularly after prior antibiotic therapy or insufficient blood volume collection (<1 mL).
- Results typically take **24–72 hours**, causing delays in initiating targeted therapy.

Automated culture systems (e.g., BacT/ALERT, BACTEC) have improved detection rates and reduced turnaround times but remain expensive and

inaccessible in many resource-limited settings.

In India, ICMR-supported hospital surveillance programs are working toward **standardizing blood culture protocols** and **enhancing microbial yield**, especially for neonatal intensive care units (NICUs).

Combined Hematological Scoring Systems

To improve diagnostic accuracy, multiple hematological parameters can be combined into a **Hematologic Scoring System (HSS)**—developed by Rodwell et al.—which assigns scores based on abnormalities in TLC, ANC, I/T ratio, platelet count, and morphological features.

- A **score ≥ 3** suggests a high probability of sepsis. This system enhances diagnostic reliability when cultures are negative but clinical suspicion is high.

Summary of Diagnostic Value of Traditional Markers

Marker	Time of Elevation	Sensitivity (%)	Specificity (%)	Comments
TLC	Variable	60	70	Poor standalone value
ANC	4–6 h	65	75	Useful with I/T ratio
I/T ratio	2–4 h	80	70	Early and sensitive
Platelet count	24–48 h	55	65	Indicator of severity
CRP	6–8 h	70–85	80–90	Best negative predictive marker
Blood culture	Variable	60–80	100	Gold standard

Traditional markers remain valuable in low-resource settings but are most effective when **interpreted collectively** rather than individually.

Emerging and Novel Biomarkers

While traditional markers provide useful screening information, they often lack the speed and precision required for early diagnosis. Consequently, extensive research has focused on **novel biomarkers** that can detect infection earlier, with higher

sensitivity and specificity. These biomarkers primarily reflect **cytokine release, cell surface activation, and molecular responses** to infection.

Procalcitonin (PCT)

Procalcitonin, a **precursor of calcitonin**, is synthesized by various tissues in response to bacterial endotoxins.

- It rises **within 2–4 hours** of infection, peaks by 12–24 hours, and declines rapidly with successful therapy.

- **Normal neonatal levels:** <0.5 ng/mL; levels >2 ng/mL suggest bacterial sepsis.

Advantages:

- Rises earlier than CRP, making it valuable for early diagnosis.
- Less likely to be elevated in viral or inflammatory conditions.
- Useful in **monitoring treatment response** and guiding antibiotic discontinuation.

Limitations:

- Physiological elevation in the first 48 hours of life may cause false positives.
- Elevated in conditions like severe respiratory distress or asphyxia.

Cytokine Markers (IL-6, IL-8, TNF- α)

Cytokines play a central role in initiating the inflammatory cascade.

- **Interleukin-6 (IL-6):** One of the earliest markers to rise—detectable within **2 hours** of infection onset. Levels >18 pg/mL suggest infection.
- **Interleukin-8 (IL-8):** Released by macrophages and endothelial cells, rises within **2–4 hours**, and correlates with sepsis severity.
- **Tumor Necrosis Factor-alpha (TNF- α):** Indicates early immune activation but is transient in circulation.

Advantages:

- Detectable much earlier than CRP and PCT.
- Particularly useful in identifying early-onset sepsis (EOS).

Limitations:

- Short half-lives require rapid sample processing.
- High testing cost and limited availability in resource-poor settings.

Cell Surface Markers

Neutrophil CD64

CD64 is a **high-affinity Fc gamma receptor** upregulated on neutrophils during bacterial infection.

- **CD64 index >2.3** is suggestive of sepsis.
- Detectable using **flow cytometry**, it offers sensitivity up to **90%** and specificity around **85%**.

Advantages: Rapid rise within 1–2 hours and correlates with infection severity.

Limitations: Requires specialized laboratory equipment.

CD11b and HLA-DR

- **CD11b** expression increases rapidly after neutrophil activation.
- **Monocyte HLA-DR** expression decreases in sepsis and may predict immune paralysis. These markers complement CD64 and improve diagnostic accuracy when used in combination.

Genetic and Molecular Markers

Advances in genomics have identified **toll-like receptor (TLR)** polymorphisms and **microRNA (miRNA)** expression profiles associated with neonatal sepsis.

- **TLR2 and TLR4 polymorphisms** alter immune recognition of Gram-positive and Gram-negative bacteria.
- **miRNA-150, miRNA-223, and miRNA-146a** have shown promise as early diagnostic indicators, regulating inflammatory gene expression.

Molecular assays such as **polymerase chain reaction (PCR)** and **nucleic acid amplification tests (NAATs)** can detect bacterial DNA directly from blood within hours, bypassing culture limitations.

Omics-Based and Metabolomic Approaches

Emerging **proteomic and metabolomic technologies** aim to detect specific molecular fingerprints of sepsis.

- **Proteomics** identifies sepsis-related proteins like haptoglobin,

apolipoproteins, and complement fragments.

- **Metabolomics** detects altered metabolic products (e.g., lactate, acylcarnitines) reflecting host-pathogen interaction.

Integration of omics data using **artificial intelligence (AI)** algorithms can develop predictive models with high diagnostic accuracy, paving the way for personalized sepsis diagnostics

Comparative Summary of Emerging Biomarkers

Biomarker	Time to Elevation	Sensitivity (%)	Specificity (%)	Clinical Relevance
Procalcitonin (PCT)	2–4 h	85–90	80–90	Early and specific marker
IL-6	2 h	90	85	Earliest cytokine response
IL-8	2–4 h	85	80	Correlates with severity
TNF- α	2–6 h	70	75	Early but transient
CD64	1–2 h	90	85	Highly specific cellular marker
miRNA panel	Variable	85–95	90	Promising research tool

Integration into Clinical Practice

Combining biomarkers from **different stages of immune activation** improves diagnostic accuracy. For example, a **triple marker combination (IL-6 + PCT + CRP)** enhances sensitivity beyond 95%. The ICMR has prioritized translational research to validate such **biomarker panels** in Indian neonatal populations, aiming for the development of **low-cost point-of-care diagnostic kits** adaptable to NICU settings.

Point-of-Care and Rapid Diagnostic Tools

Timely detection of neonatal sepsis is critical for reducing morbidity and mortality. In many resource-limited settings, including parts of India, access to sophisticated laboratory testing is restricted. Therefore, **point-of-care (POC) diagnostics** that are rapid, reliable, and affordable have gained significant attention. These innovations aim to detect infection at the bedside within minutes to hours, minimizing delays in initiating treatment.

Lateral Flow Immunoassays (LFIA)

Lateral flow assays are compact, user-friendly kits that can detect biomarkers such as **CRP, procalcitonin (PCT), or IL-6** using a drop of blood or plasma.

- Results are usually available within **15–30 minutes**.
- Modern test strips use **fluorescent or gold nanoparticle-based detection**, enhancing visual clarity and quantitative capability.

ICMR has supported several public–private partnerships in developing **low-cost CRP and PCT LFIAs** tailored to Indian NICU conditions. These devices can be operated by trained nurses or technicians, providing semi-quantitative results that guide antibiotic initiation and escalation.

Microfluidic and Lab-on-a-Chip Platforms

Microfluidic technology enables the processing of very small sample volumes (as low as 10–50 μL), which is ideal for neonates.

- These **lab-on-a-chip devices** integrate sample preparation, reaction, and

detection into a single disposable cartridge.

- They can detect multiple biomarkers simultaneously — e.g., **IL-6**, **PCT**, **CRP**, and **CD64** — within 30–60 minutes.

The **ICMR–National Institute of Pathology** and several Indian Institutes of Technology (IITs) are working on **microfluidic prototypes** for neonatal sepsis screening, aiming to produce **portable and battery-operated analyzers** suitable for rural and peripheral health centers.

Nucleic Acid-Based Rapid Tests

PCR-based and **nucleic acid amplification tests (NAATs)**, including **LAMP (loop-mediated isothermal amplification)** and **RT-PCR**, can detect bacterial DNA directly from blood samples.

- Turnaround time: **1–2 hours**.
- Sensitivity and specificity exceed **90%** for common pathogens like *Klebsiella pneumoniae*, *E. coli*, and *Staphylococcus aureus*.

Commercial multiplex PCR platforms (e.g., **BioFire FilmArray**, **Verigene**) can identify bacterial species and resistance genes simultaneously. However, these systems remain expensive. The **ICMR-AMR surveillance network** is currently evaluating **simplified PCR assays** for feasible integration into neonatal units in India.

Biosensors and AI-Enabled Detection

Recent developments combine **biosensing technology** with **artificial intelligence (AI)** and **machine learning** to predict sepsis risk based on physiological parameters (e.g., heart rate variability, oxygen saturation, and temperature). Wearable biosensors can continuously monitor newborns and alert clinicians to early signs of infection before overt clinical symptoms develop.

Pilot programs supported by the **Department of Biotechnology (DBT)** and

ICMR are validating such smart monitoring devices in select tertiary care hospitals. These tools, once standardized, could revolutionize neonatal care in both rural and urban hospitals.

Challenges and Limitations in Current Diagnostics

Despite considerable progress, diagnosing neonatal sepsis remains a major challenge, particularly in **low- and middle-income countries (LMICs)** like India. The variability in clinical presentation, laboratory availability, and microbial patterns complicates diagnostic decision-making.

Non-Specific Clinical Presentation

Neonates with sepsis often present with subtle, non-specific signs such as poor feeding, lethargy, or temperature instability. These overlap with other neonatal conditions like respiratory distress or metabolic disorders, leading to diagnostic uncertainty and frequent overuse of antibiotics.

Limitations of Current Biomarkers

Traditional biomarkers like **CRP** and **TLC** lack sufficient sensitivity and specificity to differentiate infection from inflammation. Even newer markers such as **PCT** and **IL-6** can be elevated in non-infectious conditions like asphyxia or meconium aspiration. Moreover, variations due to gestational age, birth weight, and sampling time complicate interpretation.

Infrastructural Constraints

In many NICUs, particularly in peripheral or district hospitals, access to advanced assays (e.g., cytokine panels, flow cytometry) is limited.

- **Blood culture facilities** are often unavailable or inconsistent in quality.
- **Delay in sample transport** and **inadequate blood volume collection** further reduce diagnostic accuracy.

- Lack of trained laboratory personnel contributes to errors in sample handling and reporting.

Antimicrobial Resistance (AMR) and False-Negative Cultures

High rates of antimicrobial resistance complicate both diagnosis and treatment. Prior empirical antibiotic use before culture collection can result in **false-negative blood cultures**, misleading clinicians. The ICMR's **National AMR Surveillance Network** has documented a rising prevalence of **multi-drug resistant (MDR) organisms** in neonatal sepsis, emphasizing the need for rapid diagnostics capable of detecting both pathogens and resistance determinants.

Economic and Operational Challenges

Novel diagnostic assays, though promising, remain **cost-prohibitive** for widespread implementation.

Reagent costs, calibration requirements, and dependence on imported kits limit scalability. Furthermore, lack of **regulatory approval and standardization** across laboratories prevents uniform interpretation of biomarker cut-offs.

Future Perspectives and Research Directions

The future of neonatal sepsis diagnostics lies in **integration, innovation, and implementation** — combining molecular science with bedside practicality. Continued collaboration between clinicians, researchers, and policymakers is essential to translate laboratory discoveries into clinical benefit.

Multiplex and Combined Biomarker Panels

The diagnostic accuracy of sepsis detection improves significantly when **multiple biomarkers** representing different inflammatory pathways are combined. Ongoing research supported by ICMR and DBT is evaluating panels integrating **CRP, PCT, IL-6, CD64, and miRNA profiles**, which can be incorporated into a single test

platform for higher sensitivity (>95%) and specificity (>90%).

Integration of Artificial Intelligence and Predictive Modelling

Machine learning algorithms can analyze clinical, laboratory, and physiological data to predict sepsis onset hours before clinical recognition. AI-based scoring systems (e.g., **NeoSAFE** or **NeoSepsis Index**) could guide risk stratification and antibiotic stewardship in NICUs. Collaboration between ICMR and digital health innovators is expected to lead to **AI-integrated diagnostic dashboards** tailored for Indian hospitals.

Genomic and Proteomic Research

Next-generation sequencing (NGS) and proteomic profiling offer deep insights into pathogen–host interactions.

- NGS can identify **bacterial DNA, virulence genes, and resistance determinants** in a single run.
- Proteomic studies aim to discover **specific plasma protein signatures** that can differentiate bacterial from viral sepsis.

These tools, once simplified for clinical use, could replace traditional cultures in the coming decade.

Development of Indigenous Diagnostic Kits

To ensure affordability and accessibility, the **ICMR and Government of India** have prioritized **indigenous diagnostic development** under the Make in India initiative.

- Efforts include **low-cost CRP and PCT kits, multiplex PCR panels, and rapid microfluidic cartridges** designed for rural health centers.
- National validation studies are being conducted through ICMR's **National Institute for Research in Reproductive and Child Health (NIRRCH)** and **AIIMS network hospitals**.

These initiatives will help standardize neonatal sepsis diagnosis and improve early detection across India's diverse healthcare settings.

Towards Personalized Neonatal Sepsis Management

The long-term goal is **precision neonatology**, where individual risk factors, genetic profiles, and biomarker patterns guide tailored diagnostic and therapeutic decisions.

Such an approach could minimize unnecessary antibiotic use, reduce antimicrobial resistance, and ultimately improve neonatal survival outcomes.

Conclusion

Neonatal sepsis remains a major cause of morbidity and mortality, particularly in developing countries. Early and accurate diagnosis is vital for improving survival outcomes. Traditional markers such as **TLC, I/T ratio, platelet count, and CRP** remain useful but lack sufficient sensitivity and specificity when used alone.

Emerging biomarkers like **procalcitonin, IL-6, IL-8, and CD64** offer improved early detection, while advances in **genomics, proteomics, and AI-based predictive systems** promise rapid and precise diagnosis. However, limited infrastructure and cost constraints continue to challenge their widespread use.

Efforts led by the **Indian Council of Medical Research (ICMR)** and **Government of India** toward developing affordable, point-of-care diagnostics and validating biomarker panels are vital. Integrating multiple biomarkers with modern analytical tools can significantly enhance early diagnosis, guide antibiotic stewardship, and reduce neonatal mortality.

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