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Review Article

Role of molecular diagnostics in early detection of neonatal sepsis: a narrative review

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ABSTRACT

Neonatal sepsis is a major cause of illness and death in infants across the globe, particularly in low and middle-income countries. The diagnosis of infections is important in order to provide early treatment to the patient, which may result in improved outcomes. Automated blood culture with antimicrobial susceptibility testing (AST) is considered to be the gold standard, but it has limited clinical utility due to the time required to obtain results, the sensitivity of the method in case of low bacterial loads, and previous antibiotic therapy. The review aims to critically compare the utility of molecular techniques with culture-based techniques in terms of their performance characteristics, like the time required to detect the causative agent, and their clinical utility. The existing literature is in support of the use of molecular techniques in terms of their rapidity and high specificity. Nevertheless, despite their utility, they are not suitable to be used individually, first because they cannot detect phenotypic susceptibility, and second, they may detect non-viable organisms. Therefore, it is important to have a combined approach in order to have a synergistic effect, which may result in improved therapy, enhanced antimicrobial therapy, and improved neonatal health.

Keywords: Neonatal sepsis, Molecular diagnostics, PCR, Next-generation sequencing, Biomarkers, Rapid diagnosis

INTRODUCTION

Neonatal sepsis is a major global health challenge and a significant cause of neonatal mortality, particularly in developing and underdeveloped countries. It contributes substantially to preventable deaths and morbidity worldwide. The 2016–17 global burden of disease (GBD) estimated approximately 1.3 million neonatal sepsis cases annually (≈937 per 100000 live births), while a systematic review up to May 2019 reported a pooled incidence of 2,824 per 100000 live births (95% CI: 1892-4,194).[1] Globally, nearly 3.0 million cases occur each year, resulting in 203000-570000 deaths, with neonatal sepsis accounting for about 25% of neonatal deaths in low-and middle-income countries and mortality rates ranging from 10-29%.[2]

The World Health Organization has emphasized the need for early diagnosis and timely intervention to reduce mortality associated with neonatal sepsis.[3-5] However, early diagnosis remains challenging due to nonspecific clinical manifestations such as temperature instability, poor feeding, respiratory distress, and lethargy, which overlap with non-infectious conditions.[6] Although blood culture is the reference standard, its sensitivity is limited by low bacteremia, small sample volumes, prior antibiotic exposure, and prolonged turnaround times of 48-72 hours.[7] These limitations have led to increased adoption of molecular diagnostic technologies that enable rapid pathogen identification and antimicrobial resistance detection, thereby facilitating early targeted therapy and improved outcomes. Although these techniques are costlier than conventional methods, studies suggest that they may offset costs by reducing unnecessary antibiotic

use, hospitalization duration, and infection-related complications, though neonatal-specific economic data remain.[8,9]

Despite their advantages, implementation of molecular diagnostics faces significant challenges, particularly in low-and middle-income countries, including limited laboratory infrastructure, lack of trained personnel, and high equipment and maintenance costs. Even in high-income settings, integration of molecular results into clinical workflows and their interpretation alongside culture findings can be challenging.[9-11]

Recent advances in portable and cartridge-based molecular platforms, such as genexpert and sample-to-answer polymerase chain reaction (PCR) systems, offer promising solutions by enabling rapid detection with minimal technical expertise and reduced contamination risk. Although not specifically designed for neonatal sepsis, these technologies show potential for adaptation in neonatal and pediatric settings, especially in resource-limited environments. Further research is needed to optimize these platforms for small sample volumes and expand pathogen and resistance gene detection relevant to neonatal sepsis.[11-13]

PATHOPHYSIOLOGY AND CLINICAL CHALLENGES OF NEONATAL SEPSIS

Sepsis in neonates develops from an interplay of invading pathogens and the weakened immune system of the neonate. Neonates, especially those born preterm or with low birth weight, are immunocompromised in innate and adaptive immune systems, including neutrophil storage, chemotaxis, phagocytosis, complement system functioning, and antigen-specific immunological memory. These immunological handicaps impair the ability to localize infection, leading to rapid disease spread resulting in sepsis and septic shock.[14,15] The pathophysiology of neonatal sepsis is marked by a deranged inflammatory response initiated when pathogen-associated molecular patterns recognize pattern-recognition receptors, causing uncontrolled cytokine release and endothelial dysfunction. This results in disturbances of microcirculation, metabolism, and multiple organs, often progressing rapidly without prominent clinical signs. Clinical presentation remains non-specific, with signs such as temperature changes, feed intolerance, apnea, and lethargy, making early diagnosis difficult.[16]

Clinical challenges are further compounded by heterogeneity between early onset sepsis (EOS) and late onset sepsis (LOS). EOS is commonly related to maternal genitourinary flora, whereas LOS, including healthcare-associated infections, may be community-acquired and involve multidrug-resistant microorganisms in neonates exposed to intensive care settings, complicating standardization of infections.[17] Another major challenge is distinguishing true infection from non-infectious inflammatory conditions common in neonates, such as respiratory distress syndrome or birth stress. Traditional markers like C-reactive protein and procalcitonin lack adequate specificity, leading to improper and prolonged antibiotic use, increased resistance, and alteration of neonatal flora, ultimately affecting long-term outcomes.[18,19]

CONVENTIONAL DIAGNOSTIC METHODS AND THEIR LIMITATIONS

Blood culture

Blood culture is considered the gold standard for microbiological diagnosis of neonatal sepsis as it enables identification of causative pathogens and their antibiotic susceptibility. However, its performance in neonates is limited due to biological and technical factors. Sensitivity is generally low and variable (50-80%), influenced by blood volume, timing of sampling, and prior antibiotic administration. Low-level bacteremia further reduces sensitivity, and although higher blood volume improves yield, obtaining adequate volume in preterm infants is difficult. Empirical antibiotic use before sampling also decreases positivity rates.[20]

Specificity is usually high (>95%) since isolation of a true pathogen from a sterile site confirms infection; however, contamination by skin commensals such as coagulase-negative staphylococci may lead to false-positive results and unnecessary antimicrobial exposure. Another major limitation is prolonged turnaround time, with detection requiring 24-72 hours followed by additional time for identification and susceptibility testing. This delay interferes with early therapeutic optimization and contributes to prolonged broad-spectrum antibiotic use, antimicrobial resistance, and disruption of the neonatal microbiome.[7,21]

Hematological and biochemical markers

Hematological and biochemical indices have been employed as ancillary methods for the early screening and supportive diagnosis of neonatal sepsis. The commonly employed biomarkers include C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and hematological parameters such as the immature to total ratio of neutrophils (I/T ratio). Although these tests are readily available and offer rapid results, their diagnostic accuracy is variable, and none of them can individually confirm or rule out the diagnosis of sepsis.[22]

C-reactive protein

C-reactive protein (CRP) is the most commonly employed acute-phase protein in neonatal intensive care units. The sensitivity of CRP in early infection is low because CRP concentrations begin to rise 6-12 hours post-infection and reach a peak at 24-48 hours post-infection. The sensitivity of CRP has been reported to range from 60% to 90%, while specificity has been reported to range from 70% to 85%,

depending on the time of measurement, the technique of measurement, and the criteria used for measurement. Repeated measurements of CRP are more useful than a single measurement. However, CRP can also be elevated in non-infectious inflammatory conditions such as birth asphyxia, meconium aspiration syndrome, intraventricular hemorrhage, or maternal fever, thus lowering its specificity.[23,24]

Procalcitonin

Procalcitonin (PCT) is thought to be more specific than CRP for bacterial infection and tends to rise earlier (within 2-4 hours). Sensitivity has been reported to vary from 70% to 95%, with specificity from 70% to 90%. Nevertheless, its use in neonates is made difficult by the physiological increase in the first 24-48 hours of life, especially in preterm infants, which reduces its value in the diagnosis of early sepsis.[25]

Interleukin-6

Interleukin-6 (IL-6) is a pro-inflammatory cytokine with early sensitivity that rises quickly following microbial invasion and can show high early sensitivity (up to 80-100%). However, its short half-life causes it to fall quickly after peaking, making it less reliable as a standalone diagnostic tool. Additionally, variability in testing and lack of availability make it less ideal for common use. The addition of IL-6 to CRP or PCT improves diagnostic accuracy.[26]

Immature to total neutrophil ratio (I/T ratio)

The I/T ratio is a simple and cost-effective hematological marker. The sensitivity of the I/T ratio varies from 60% to 90%, and the specificity varies from 50% to 80%. Although an elevated I/T ratio can help in diagnosing sepsis, it is not a specific marker since perinatal stress, maternal hypertension, prolonged labor, or any other inflammatory process can also raise the immature neutrophil count.[27]

In summary, although hematological and biochemical markers are useful ancillary tools, particularly when used in a serial or combined fashion, they have been shown to have suboptimal specificity and variable sensitivity for early infection. Therefore, they cannot be used as a substitute for microbiological confirmation but may have a role in early risk stratification and antimicrobial therapy.

MOLECULAR DIAGNOSTIC TECHNIQUES IN NEONATAL SEPSIS

PCR-based methods

PCR-based approaches have greatly improved the diagnostic workup of neonatal sepsis by allowing for the rapid and culture-free identification of microbial DNA directly from blood specimens. These approaches are especially helpful in neonates, in whom low-level bacteremia, small volumes of blood, and previous antibiotic therapy often reduce the sensitivity of blood cultures.

Conventional PCR

Conventional (end-point) PCR uses specific primers to amplify targeted DNA sequences and has been applied in neonatal sepsis for detection of pathogens such as group B *Streptococci*, *Escherichia coli*, and *Staphylococcus aureus*. Compared with blood culture, it may show higher analytical sensitivity, particularly in antibiotic-exposed patients.[28]

However, it is generally limited to single-or multi-target detection, provides only qualitative results, and requires post-PCR processing such as gel electrophoresis, increasing contamination risk and turnaround time. Sensitivity varies widely (approximately 60-95%) depending on pathogen load and test format, while high specificity (>90%) is achievable when contamination is avoided.[7,21]

Real-time PCR

Real-time PCR, also known as quantitative PCR (qPCR), is a major improvement over standard PCR. It allows for the real-time measurement of the amount of amplified DNA in a closed system with fluorescent probes. This minimizes the risk of contamination and shortens the time required for the procedure. Along with advantages and there are some disadvantages which are illustrated in Figure 1.

Multiplex PCR and syndromic panels

The multiplex PCR platforms are a significant improvement over the older technologies and enable the detection of multiple bacterial, viral, and fungal pathogens simultaneously from a small volume of blood, which is a critical consideration in neonates.

The commercially available syndromic panels are capable of detecting 15-30+ pathogens in about 1-5 hours. The specificity is generally very high (>95%), while the sensitivity is pathogen and load-dependent (generally 80-95%).[29,30]

One of the most important benefits of multiplex platforms is the presence of antimicrobial resistance genes, including: mecA/mecC - methicillin resistance, vanA/vanB - vancomycin resistance, ESBL-associated genes like, blaCTX-M, carbapenemase genes like KPC, NDM, OXA-48.

Early detection of resistance genes facilitates rapid antimicrobial optimization and enhanced stewardship strategies. Research has shown decreased times to appropriate therapy and potential decreased exposure to

broad-spectrum antibiotics when multiplex PCR data are incorporated into clinical practice.[8,29] However, several key limitations exist: Detection restricted to organisms in the panel, Risk of overdiagnosis due to the detection of non-viable DNA, High cost and infrastructure requirements, Inadequate antimicrobial susceptibility profiling.

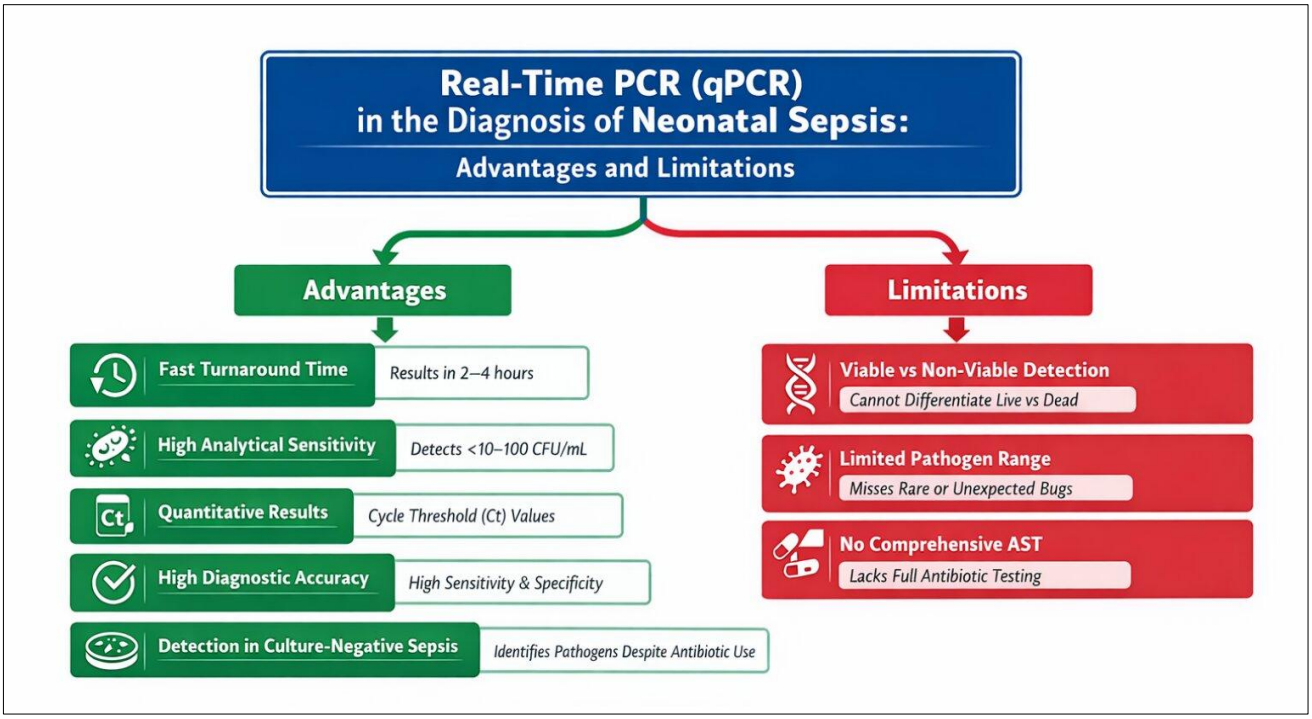

Figure 1: Advantages and limitations of real-time PCR (qPCR) in the diagnosis of neonatal sepsis.

Clinical impact and integration

The time to pathogen identification is reduced with PCR-based diagnostics compared to conventional blood culture (24-72 hours). In the NICU setting, earlier identification could potentially allow for: Targeted therapy, de-escalation of broad-spectrum antibiotics, decreased pressure on antimicrobial resistance, shorter hospital stays in selected patients.

However, at present, there is evidence to support their use as adjunctive tests, rather than replacing culture, as blood culture is still required for comprehensive antimicrobial susceptibility testing and epidemiological studies.[7,30]

Next-generation sequencing

Metagenomic next-generation sequencing (mNGS) is a culture-free molecular diagnostic tool that enables comprehensive and unbiased detection of microbial DNA or RNA directly from clinical samples. Unlike PCR-based methods, it does not require prior knowledge of the target organism and can simultaneously detect bacteria, viruses, fungi, and parasites. In neonatal sepsis, mNGS is particularly useful in culture-negative cases, especially when blood cultures are affected by prior antibiotic exposure or when pathogens are unusual, fastidious, or uncultivable. Studies indicate that mNGS improves pathogen detection compared to conventional techniques and may support earlier optimization of antimicrobial therapy.[31,32] In addition to pathogen identification, mNGS can detect antimicrobial resistance (AMR) genes, providing early insights into resistance mechanisms before phenotypic susceptibility results are available, which is critical in NICU settings with rising multidrug-resistant organisms. However, its clinical use is limited by several challenges: high cost of sequencing platforms and reagents, longer turnaround time compared to rapid PCR tests, requirement for specialized bioinformatics support, difficulty distinguishing true pathogens from contaminants or colonizers, lack of standardized workflows and interpretation criteria.

Interpretation is further complicated in neonates due to low microbial load and background contamination affecting specificity. Thus, although mNGS represents a major advancement, it is currently best used as a complementary or problem-solving tool, particularly in critically ill neonates with culture-negative sepsis.

Microarray technologies

The microarray-based diagnostic system relies on immobilized oligonucleotide probes to enable simultaneous analysis of multiple pathogen-specific nucleic acid sequences or host immune response gene expression profiles in a single clinical sample. Its high-throughput nature allows simultaneous analysis of multiple microbial targets and immune response markers,

making it an important component of syndromic diagnostic strategies.

In neonatal sepsis, microarray technology has been explored primarily for two important applications. First, it enables multiplex pathogen detection by simultaneously identifying a broad spectrum of bacterial, viral, and, in some cases, fungal pathogens through the use of predefined probe sets. This approach allows rapid and comprehensive pathogen screening from a single clinical sample. Second, microarrays have been utilized for host gene expression profiling, which focuses on analyzing the infant's immune response rather than directly detecting pathogens. By evaluating specific patterns of gene expression, this technique can help distinguish bacterial infections from viral infections, thereby improving diagnostic accuracy and supporting timely clinical decision-making.

Host response microarray analyses have demonstrated the ability to differentiate bacterial from viral infections with high diagnostic accuracy, which is particularly important in neonates where clinical presentation is often nonspecific and unnecessary antibiotic use contributes to antimicrobial resistance and microbiome dysbiosis. Gene expression-based classifiers described by Tsalik et al show strong discriminatory power, supporting transcriptome profiling as a diagnostic tool.[33] Multiplex molecular assays, including microarray-based platforms, offer several advantages and limitations in neonatal sepsis diagnosis, as summarized in Table 1.

Emerging molecular and host-response biomarkers

Recent progress in the fields of transcriptomics, proteomics, metabolomics, and microRNA (miRNA) profiling has made it possible to identify host response signatures that can enhance the diagnostic accuracy of neonatal sepsis. Unlike traditional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT), emerging molecular biomarkers have the potential to distinguish between infectious and non-infectious systemic inflammation, bacterial and viral infections, and predict disease severity and outcome.

Transcriptomic signatures

Host transcriptome profiling is a method that assesses gene expression patterns in peripheral blood leukocytes. Several studies have shown that RNA expression signatures can be used to accurately distinguish bacterial infection from sterile inflammation and viral infection. These tools are especially useful in neonates, in whom clinical manifestations are subtle and non-specific.

For instance, host gene expression signatures reported by Tsalik et al showed excellent discriminatory ability in distinguishing infectious causes.[33] Similarly, progress in clinical metagenomics and host response profiling reported by Chiu et al illustrate the combined use of pathogen detection and host transcriptional analysis as a promising approach to precision medicine.[32]

In neonatal cohorts, transcriptomic biomarkers such as IL-6 gene pathway-related transcripts, interferon-stimulated genes, and neutrophil activation transcripts have been explored for their potential in early diagnosis and risk assessment.

Proteomic biomarkers

Proteomic analysis has emerged as a valuable approach for identifying biomarkers associated with neonatal sepsis by enabling the comprehensive measurement of plasma proteins involved in inflammatory and immune responses. While conventional biomarkers such as CRP and procalcitonin (PCT) continue to be widely used in clinical practice, several novel protein biomarkers have shown promise for improving the early diagnosis and prognosis of sepsis. These include presepsin (soluble CD14 subtype), which reflects monocyte and macrophage activation; serum amyloid A, an acute-phase protein that increases rapidly during infection; lipopolysaccharide-binding protein, which plays a key role in the host response to gram-negative bacterial infections; and pro-adrenomedullin, a biomarker associated with endothelial dysfunction and disease severity. The identification and validation of these biomarkers may enhance the accuracy of neonatal sepsis diagnosis and facilitate timely therapeutic interventions.

Proteomic biomarker panels may offer improved diagnostic performance when analyzed in combination rather than individually. Multiplex protein analysis is being increasingly explored for risk assessment and mortality prediction in neonatal sepsis.

MicroRNA profiling

Circulating microRNAs (miRNAs) are small, non-coding RNA molecules involved in post-transcriptional regulation of gene expression and play a major role in immune and inflammatory responses. Several miRNAs, including miR-16, miR-146a, and miR-155, are involved in key inflammatory signaling pathways and have emerged as promising candidates for early detection of neonatal sepsis, as they regulate innate immune responses, cytokine production, and pathogen recognition.

A major advantage of miRNA diagnostics is their stability in biological fluids such as plasma or serum due to resistance to enzymatic degradation. In addition, miRNA profiling requires only small sample volumes, making it suitable for neonatal diagnostics. Recent studies indicate that specific miRNA expression patterns can differentiate septic neonates from non-infected controls with high diagnostic accuracy, supporting their role as non-invasive and rapid diagnostic tools.[34,37]

However, challenges remain, including variability in miRNA expression profiles, lack of standardized detection methods, and limited validation in large-scale neonatal clinical trials.

Table 1: Advantages and limitations of multiplex molecular assays (including microarray-based platforms) for the diagnosis of neonatal sepsis in clinical settings.

Advantages	Disadvantages	References
High multiplexing capability	Requirement for predefined probe sets, resulting in reduced ability to detect novel or unexpected pathogens	34
Concurrent pathogen and host response analysis	Lower analytical sensitivity compared to some real-time PCR and next-generation sequencing platforms	35
Potential decrease in unnecessary antibiotic use through targeted therapy	Relatively high cost and technical complexity, limiting routine clinical use	34,36
Standardized and automated processing in some commercial platforms	Limited validation in large-scale neonatal populations	35

Integrative multi-omic approaches

The future of neonatal sepsis diagnosis lies in the integration of multiple omics technologies, commonly referred to as multi-omic integration. This comprehensive approach combines advanced pathogen detection methods, such as polymerase chain reaction (PCR) and metagenomic next-generation sequencing (mNGS), with host transcriptomic signatures that reflect the immune response to infection. In addition, proteomic and metabolomic biomarkers provide valuable insights into the physiological and biochemical changes associated with sepsis, while antimicrobial resistance gene profiling enables the rapid identification of resistance determinants that may influence treatment decisions. By integrating these diverse datasets, multi-omic platforms have the potential to improve diagnostic accuracy, facilitate early detection, distinguish infectious from non-infectious conditions, and support personalized therapeutic strategies in neonatal sepsis management.

Such integrated platforms are envisioned to offer rapid etiologic diagnosis and immune response profiling, which would enable individualized antimicrobial therapy and improved prognostic capabilities. Recent reviews have underlined the fact that the integration of pathogen detection with host response profiling could potentially improve the sensitivity and specificity of the test compared to single-modality testing.[38]

However, certain challenges still exist, such as high cost, the need for advanced bioinformatics support, the lack of large-scale neonatal validation studies, and the absence of standardized clinical cut-offs.

ADVANTAGES OF MOLECULAR DIAGNOSTICS

Molecular diagnostic approaches have several key advantages over traditional culture-based approaches in the diagnosis of neonatal sepsis. Firstly, they allow for rapid turnaround times, with results available in hours rather than days, and thus enable earlier treatment escalation or de-escalation. They also have greater analytical sensitivity, especially in neonates with low bacteremia or previous exposure to antibiotics, in whom blood cultures are often falsely negative. Molecular approaches such as real-time PCR and metagenomics allow for direct pathogen detection without the need for viable organisms, thus improving pathogen identification. Molecular approaches also enable the simultaneous identification of multiple pathogens and resistance genes, thus facilitating targeted therapy and antimicrobial stewardship. Newer approaches that combine pathogen identification with host response profiling further improve diagnostic accuracy by distinguishing infectious from non-infectious inflammation. Molecular diagnostics, therefore, help improve clinical decision-making and reduce unnecessary exposure to antibiotics, and may potentially improve neonatal outcomes, especially in high-risk intensive care units.[39]

LIMITATIONS AND CHALLENGES

Notwithstanding their diagnostic benefits, molecular diagnostic approaches for neonatal sepsis have important limitations. A major limitation is the high cost of equipment, reagents, and maintenance, requiring sophisticated laboratory facilities, which limits feasibility in many settings. Additionally, technical expertise and bioinformatics support are required, especially for complex platforms such as multiplex PCR panels and next-generation sequencing.[40]

Another limitation is the potential for contamination, particularly in low-biomass neonatal blood samples, which may result in false-positive results and unnecessary antimicrobial use. Moreover, as molecular tests are independent of microbial viability, interpretation may be difficult in cases of colonization, contamination, or transient DNAemia rather than invasive infection, making it challenging to distinguish true pathogens from commensals without clinical correlation.[7]

Finally, these approaches remain largely inaccessible in resource-poor settings where the burden of neonatal sepsis is highest.

CONCLUSION

Neonatal sepsis is a critical concern for morbidity and mortality, highlighting the need for timely and accurate diagnostic tools. The current gold standard, blood culture, is limited by prolonged turnaround time, reduced sensitivity in mild bacteremia, and decreased yield following antibiotic exposure. Although automated blood culture systems improve detection rates and reduce time to positivity, they still depend on viable organisms and require additional time for identification and susceptibility testing.

The advent of advanced diagnostic techniques, including real-time PCR, multiplex syndromic testing, microarray technology, and next-generation sequencing, has revolutionized microbiological diagnostics. These methods enable rapid, sensitive, and culture-independent detection of pathogens, including simultaneous identification of multiple organisms. Additionally, biomarkers such as transcriptome, proteome, and microRNA help distinguish between infectious and non-infectious conditions.

However, these technologies are limited by high cost, need for technical expertise, and complex interpretation, emphasizing the need for an interdisciplinary approach.

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