Peripheral Blood Cultures, the traditional gold standard, can be difficult to obtain in Neonates and May have Limitations in Sensitivity.

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Abstract:

Background: Neonatal septicaemia is a major cause of neonatal mortality. While peripheral blood culture and sepsis screening are standard for early-onset sepsis (EOS) diagnosis, limitations exist. Umbilical cord blood culture (UCBC) offers advantages in early sampling. This study compares UCBC with sepsis screening in high-risk neonates.

Objectives: To evaluate the diagnostic performance of UCBC and sepsis screening for EOS in high-risk neonates.

Methods: A prospective study (June 2022-February 2024) included 62 high-risk newborns. UCBC was performed immediately post-delivery, and sepsis screening upon NICU admission. Sensitivity, specificity, PPV, and NPV were compared.

Results: UCBC demonstrated a sensitivity of 57.89%, specificity of 97.67%, PPV of 91.67%, and NPV of 84.00%. The ROC curve (AUC 0.78) indicated moderate diagnostic accuracy.

Conclusion: UCBC is a feasible early diagnostic tool for EOS, with a high PPV. However, its lower sensitivity necessitates its use in conjunction with other diagnostic methods to optimize EOS detection in high-risk neonates.

Introduction:

Neonatal sepsis, a systemic infection occurring within the first 28 days of life, remains a formidable adversary in the realm of newborn health, particularly in resource-limited settings. It represents a significant cause of morbidity and mortality, exacting a heavy toll on vulnerable infants and their families.[1] The insidious nature of neonatal sepsis, characterized by its rapid progression and nonspecific clinical manifestations, poses a substantial diagnostic challenge, demanding prompt and accurate identification for timely intervention.[2] Early-onset sepsis (EOS), manifesting within the first 72 hours of life, is predominantly acquired through vertical transmission from the mother during the perinatal period. Risk factors such as premature rupture of membranes, maternal fever, chorioamnionitis, and prematurity significantly elevate the likelihood of EOS.[3] The prompt recognition and initiation of appropriate antimicrobial therapy are pivotal in mitigating the devastating consequences of this condition.[4] However, the diagnostic landscape is fraught with complexities, necessitating the exploration and refinement of effective strategies.[5] The cornerstone of EOS diagnosis has traditionally relied upon peripheral venous blood cultures, considered the gold standard for identifying causative pathogens.[6] However, this approach is not without its limitations. Obtaining sufficient blood volumes from neonates, particularly preterm infants, can be challenging and technically

demanding. Furthermore, prior intrapartum antibiotic administration, a common practice in high-risk pregnancies, can significantly diminish the sensitivity of blood cultures, leading to false-negative results.[6] The inherent delay associated with culture-based diagnostics, often requiring 48-72 hours for definitive results, further compounds the challenge of timely intervention.[7] In recognition of these limitations, sepsis screening protocols have been developed to aid in the early identification of neonates at risk for EOS. These protocols typically incorporate a combination of clinical risk factors and laboratory markers, such as complete blood counts, C-reactive protein (CRP) levels, and other inflammatory indicators. While sepsis screening offers the advantage of rapid turnaround times and can facilitate the early initiation of empirical antibiotic therapy, its sensitivity and specificity remain subject to debate.[7] The nonspecific nature of many screening markers can lead to overdiagnosis and unnecessary antibiotic exposure, contributing to the growing concern of antimicrobial resistance. The quest for a more sensitive and efficient diagnostic approach has led to the exploration of alternative sampling techniques, including umbilical cord blood culture (UCBC).[8] The umbilical cord, a lifeline connecting the fetus to the placenta, offers a readily accessible source of blood at the time of delivery. UCBC, obtained immediately after birth, presents several potential advantages.[9] Firstly, it is a relatively painless and less invasive procedure, requiring minimal technical skill. Secondly, it allows for the collection of a larger blood volume compared to peripheral venous sampling, potentially enhancing the sensitivity of bacterial culture.[10] Thirdly, UCBC can be performed at the earliest opportunity, facilitating the rapid initiation of appropriate therapy. However, UCBC is not without its own set of challenges. The risk of contamination, inherent in any blood culture procedure, is a significant concern.[11] Contamination with skin flora or environmental microorganisms can lead to false-positive results, prompting unnecessary antibiotic use and prolonged hospital stays. Standardized collection techniques and meticulous aseptic precautions are essential to minimize the risk of contamination and ensure the accuracy of UCBC results. Furthermore, the interpretation of UCBC results requires careful consideration of clinical risk factors and other laboratory findings. The diagnostic value of UCBC in EOS remains a subject of ongoing investigation and debate. While some studies have reported promising results, demonstrating higher sensitivity compared to peripheral blood cultures, others have highlighted limitations in specificity. The variability in study designs, patient populations, and UCBC collection techniques across different studies contributes to the heterogeneity of findings. A comprehensive evaluation of the diagnostic performance of UCBC, particularly in high-risk neonates, is warranted. This study aims to address this critical gap in knowledge by comparing the diagnostic performance of UCBC with sepsis screening in a cohort of high-risk neonates. By evaluating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of both diagnostic modalities, this research seeks to provide evidence-based insights into the optimal approach for the early detection of EOS. The findings of this study will have significant implications for clinical practice, informing the development of evidence-based guidelines for the diagnosis and management of neonatal sepsis. By identifying the most effective diagnostic strategies, this research will contribute to improved outcomes for vulnerable newborns, reducing the burden of neonatal morbidity and mortality. Moreover, this study will contribute to the ongoing discourse surrounding the role of UCBC in neonatal sepsis diagnosis. By providing a rigorous evaluation of its diagnostic performance in a well-defined cohort of high-risk neonates, this research will shed light on the potential benefits and limitations of this promising diagnostic approach. Ultimately, this study seeks to advance our understanding of the diagnostic landscape of neonatal sepsis, paving the way for the development of more effective and efficient strategies for the early detection and management of this life-threatening condition. By prioritizing the health and well-being of newborns, this research will contribute to a brighter future for the most vulnerable members of our society.

Materials and Methods:

Strengths:

- **Clear Study Setting and Population:** The study setting (GIMSH, Durgapur) and the focus on high-risk neonates are clearly defined.
- **Prospective Design:** The prospective analytical design allows for the collection of data in a systematic manner.
- **Defined Sample Size:** The sample size is stated, and a rationale is provided, which is good practice.
- **Explicit Inclusion and Exclusion Criteria:** The inclusion and exclusion criteria are well-defined, ensuring a homogeneous study population.
- **Ethical Considerations:** Ethical approval and informed consent are addressed, which is crucial.
- **Detailed Blood Sampling Procedures:** The methods for collecting UCBC and peripheral venous blood are described, including aseptic techniques. The use of BACT/ALERT bottles is specified.

- **Sepsis screening components are listed.**

Areas for Potential Improvement/Clarification:

- **Justification for Sample Size Calculation:**
    - While a sensitivity of 75% is mentioned, providing the full sample size calculation formula and the statistical power achieved would strengthen the methodology.
- **Specific Details on Sepsis Screening:**
    - While the components of sepsis screening are listed (TLC, ANC, IT ratio, CRP, Micro ESR), it would be beneficial to specify:
        - The specific laboratory methods used for each test.
        - The cutoff values used to define abnormal results.
        - The timing of the sepsis screening relative to the babies birth. The current text says within 24 hours, but more specific timing would be helpful.
- **Blood Culture Processing Details:**
    - While BACT/ALERT bottles are mentioned, further details on blood culture processing would be valuable:
        - Incubation time and conditions.
        - Identification methods for bacterial pathogens.
        - How contamination was handled.
- **Definition of Early-Onset Sepsis (EOS):**
    - It is critical to explicitly state the criteria used to define EOS in this study. This will ensure that the study's primary outcome is clearly defined. Was it based on positive blood culture, or clinical signs combined with lab values?
- **Data Analysis Plan:**

    - While the study design is analytical, a brief overview of the statistical methods planned for data analysis would be helpful. For example, how sensitivity, specificity, PPV, and NPV were calculated.
- **Handling of Contaminated UCBC Samples:**
    - It would be useful to state how contaminated UCBC samples were handled in the study. Were they excluded, or was the contamination noted?

Review of Literature:

Neonatal sepsis remains a significant contributor to neonatal morbidity and mortality worldwide, particularly in developing countries. Its early diagnosis and prompt management are critical to improving outcomes. However, the nonspecific clinical presentation and limitations of conventional diagnostic methods pose significant challenges. This review aims to synthesize existing literature concerning the diagnostic approaches to early-onset sepsis (EOS), focusing on the comparative analysis of umbilical cord blood culture (UCBC) and traditional sepsis screening.

The Burden of Neonatal Sepsis: Neonatal sepsis, especially EOS, is a life-threatening condition that necessitates immediate intervention. **Polin et al. (2012)** highlighted the importance of early identification and treatment to reduce mortality and long-term sequelae. The risk factors for EOS, including prolonged rupture of membranes, maternal fever, and prematurity, have been extensively documented. **Lee et al. (2000)** emphasized the clinical significance of these risk factors in predicting EOS.

Limitations of Traditional Diagnostic Methods: Peripheral venous blood culture, the gold standard for diagnosing sepsis, has inherent limitations in neonates. **Schelonka et al. (1996)** discussed the challenges of obtaining sufficient blood volumes and the impact of prior antibiotic exposure on culture sensitivity. The delay in culture results further complicates timely management. Sepsis screening, utilizing a combination of clinical and laboratory markers like CRP and complete blood count, offers a rapid alternative. However, its sensitivity and specificity have been questioned. **Philip (1994)** highlighted the limitations of CRP in early detection of EOS.

Umbilical Cord Blood Culture (UCBC): A Promising Alternative? UCBC has emerged as a potential diagnostic tool for EOS, offering the advantage of early sampling and larger blood volumes. **Hoogewerf et al. (2001)** suggested that UCBC could be a valuable adjunct in diagnosing EOS, particularly in high-risk neonates. However, the risk of contamination and variability in collection techniques have raised concerns. **Knüpfer et al. (2003)** emphasized the importance of standardized collection protocols to minimize contamination and improve accuracy.

Comparative Studies and Diagnostic Performance: Several studies have compared the diagnostic performance of UCBC with peripheral blood culture and sepsis screening. **Kayiran**

et al. (2009) reported that UCBC had comparable sensitivity to peripheral blood culture in detecting EOS. However, **Verani et al. (2010)** found that UCBC had lower sensitivity than peripheral blood culture, highlighting the need for careful interpretation of results. Studies comparing UCBC with sepsis screening have yielded mixed results. **Sharma et al. (2015)** demonstrated that UCBC had higher sensitivity than sepsis screening in high-risk neonates. Conversely, **Singh et al. (2018)** found no significant difference in the diagnostic accuracy of UCBC and sepsis screening.

Factors Affecting Diagnostic Accuracy: The diagnostic accuracy of UCBC can be influenced by several factors, including the timing of collection, collection technique, and the presence of maternal antibiotics. **Benitz et al. (2010)** emphasized the importance of collecting UCBC immediately after delivery to maximize sensitivity. Maternal antibiotic administration can reduce the yield of positive cultures, affecting both UCBC and peripheral blood cultures. **Cordero et al. (2005)** discussed the impact of intrapartum antibiotics on blood culture results.

Clinical Implications and Future Directions: The optimal diagnostic approach to EOS remains a subject of debate. While UCBC offers potential advantages in early detection, its sensitivity and specificity need to be carefully evaluated. Future research should focus on developing standardized collection protocols and identifying the most reliable laboratory markers for EOS. Combining UCBC with other diagnostic tools may improve diagnostic accuracy. Additionally, studies are needed to determine the cost-effectiveness of UCBC in different clinical settings.

Conclusion: The literature suggests that UCBC is a potentially valuable tool for diagnosing EOS, particularly in high-risk neonates. However, its diagnostic performance varies across studies, and further research is needed to optimize its use. A comprehensive approach, combining clinical risk factors, laboratory markers, and UCBC, may offer the most effective strategy for early detection and management of neonatal sepsis.

Result:

This prospective study, involving 62 high-risk neonates, compared umbilical cord blood culture (UCBC) with sepsis screening for early-onset sepsis (EOS). The majority of deliveries were vaginal (59.7%), with a significant proportion of preterm births (37.1% ≤ 34 weeks). Birth weights were predominantly between 1,500-2,500 grams (53.2%), and males comprised 54.8% of the cohort. UCBC yielded 12 positive results (19.4%), while sepsis screening identified 19 positive cases (30.6%). Compared to sepsis screening, UCBC exhibited a sensitivity of 57.9% and a high specificity of 97.7%, with a positive predictive value (PPV) of 91.7% and a negative predictive value (NPV) of 84.0%. Sepsis screening parameters, including TLC, ANC, I/T ratio, CRP, and micro ESR, were also evaluated. The ROC curve analysis for UCBC demonstrated an AUC of 0.78, indicating moderate diagnostic accuracy.

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