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CORRESPONDENCE

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Culture-free biphasic approach for early sepsis detection: A true game changer

Sepsis is a life-threatening clinical syndrome that can be defined as infection-induced physiologic, pathologic, and biochemical abnormalities—the source of which may be a bacteria, virus, fungus, or parasite. According to the Global Burden of Diseases (GBD) data, there were an estimated 48.9 million cases and 11 million deaths due to sepsis worldwide in 2017, thereby making it one of the deadliest conditions.[1] Moreover, when the infection is initially detected, even a mild degree of organ failure is linked to an in-hospital death rate of more than 10%.[2] Particularly, in the event of septic shock, a 7.6% increase in mortality is observed for every hour that passes without proper antimicrobial therapy.[3] It is also worth noting that those that survive sepsis may be prone to long-standing adversities that involve physical, psychological, and cognitive impairments.[2] Thus, early diagnosis of the condition, followed by timely treatment, is crucial.

Currently, the isolation of pathogens through blood culture is recognized as the "gold standard" for diagnosing bloodstream infections (BSI) such as sepsis. Detecting a confirmed negative culture may take up to 5 days; thus, broad-spectrum antibiotic therapy is recommended until the sensitivities of cultured pathogens are characterized. Alarmingly, 40%–50% of patients with BSIs are administered inappropriate antibiotic therapy during the empirical treatment period before diagnostic test results are available. Incorrect treatments coupled with a long time-to-diagnosis may result in drug toxicity, antimicrobial-resistant bacterial strains, increased length of stay, and increased overall medical expenditures for both the patient and healthcare provider.[4-6] Additionally, a vast selection of 170 biomarkers have been identified for sepsis detection; however, none possesses 100% specificity for sepsis.[6] Since sepsis has high short-term mortality and challenging diagnosis, an alternative quick and reliable diagnostic method has been sought after for a long time. In a recent study by Ganguli et al.,[7] researchers tackled the issue of sensitivity and time efficiency drawbacks in current blood processing modules by employing a novel qualitative method that involved drying up blood at high temperatures, resulting in the creation of porous networks within the dried blood matrix which, in turn, facilitated the access of the polymerase to the DNA of pathogens, thereby enabling the amplification process to commence with the aid of primers and enzymes. Methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA), gram-negative *Escherichia coli*, and the fungus *Candida albicans* were the four bloodstream infection cause that the team was able to identify. They cross-checked the accuracy of their approach against the findings of 63 clinical samples (100% sensitivity and specificity) to identify sepsis. These samples, which were discarded whole-blood, were obtained from patients in Carle Foundation Hospital's emergency department after an institutional review board approval. Besides an increase in sensitivity, the most important implication of the study is the significantly reduced sample-to-result time from over 20 h to less than 2.5 h as shown in Table 1.[7]

In conclusion, this culture-free biphasic molecular diagnostic approach towards sepsis has paved a new era in drastically improving patient care by enabling clinicians to prescribe treatments faster, thereby alleviating antibiotic resistance and reducing mortality caused by sepsis worldwide. There is optimism that this technique will be incorporated into the clinical workflow as this approach not only significantly lowers the instrumentation complexity and response time but also improves reliability, sensitivity, and specificity.[4] However, this study was successful in identifying only four causes of bloodstream infections. Further studies and trials on large groups could help bring another breakthrough by detecting the vast array of unknown and emerging sepsis-causing pathogens and can prove to be a successful alternative to blood processing and blood-based diagnostics in bloodstream infections, leading to a more effective sepsis treatment.

TABLE 1 Table demonstrating the efficacy of culture-free biphasic approach for sepsis detection.

Pathogen identification time	2.2 h
Sensitivity	100% (95% CI; 75.29%–100%)
Specificity	100% (95% CI; 92.29%–100%)
Volume of sample	Up to 5 mL
Positive predictive value	Not reported
Negative predictive value	Not reported

Abbreviation: CI, confidence interval.

KEYWORDS

culture-free biphasic molecular diagnosis, early diagnosis, sepsis, septic shock

AUTHOR CONTRIBUTIONS

Hasan Mushahid: Conceptualization; writing—original draft. **Sanila Mughal**: Writing—original draft. **Muhammad Owais Sonija**: Writing—original draft. **Ayesha Liaquat**: Writing—review & editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author Sanila Mughal affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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