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DIAGNOSIS AND MANAGEMENT MOLECULER DETECTION OF BLOODSTREAM INFECTION

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ABSTRACT

Backround: *Examination for diagnosing sepsis or blood infections is conducted through blood culturing but this methode has several drawbacks such as a rather long incubation time.*
Objective*: This research aims to analysis of literature review to delve deeper into the potential and challenges of molecular diagnosis for blood infections or sepsis based on previous research findings.*
Methods: *This Literature Review method was conducted using electronic databases including several databases such as Google Scholar, PubMed, and Semantic Schoolar.*
Results: *Based on the research, author get 8 journal that were discuccion in this journal. Molecular detection has potential function tn the future but research on the limitations of the method and optimization of PCR methods for detecting pathogens in the blood needs further investigation.*
Conslusion: *Examination of pathogens causing bloodstream infections using PCR methods holds promising potential for the future. However, research on the limitations of the method and optimization of PCR methods for detecting pathogens in the blood needs further investigation.*

INTRODUCTION

Blood infection or sepsis is one of the serious medical challenges that affect various aspects of the healthcare population, particularly the elderly, very young, infants, pregnant women, and significance in critical care settings (Gotts & Matthay, 2016; Kern & Rieg, 2020). Globally, sepsis accounts for 20% of deaths in the Intensive Care Unit (Rudd et al., 2020). Interestingly, the prevalence of sepsis-related mortality in Indonesia exhibits a wide range, spanning from 22.5% to 52%, reflecting the complexity

of its management and the need for effective strategies tailored to regional healthcare dynamics (Purba et al., 2020; Yuniar et al., 2023).

Sepsis a condition triggered by the invasion of pathogens such as bacteria, viruses, or fungi into the bloodstream, incites a systemic inflammatory response that can have devastating consequences, often leading to mortality (Ackerman et al., 2021; Gyawali et al., 2019; Harris & Rondina, 2016). This intricate interplay between infection and inflammation underscores the urgency of advancing sepsis detection, diagnosis, and treatment.

At present, the gold standard examination for diagnosing sepsis or blood infections is conducted through blood culturing (Ahmad et al., 2017; Tjandra et al., 2022; Trung et al., 2019). This method is relatively easy to perform and has a fairly good sensitivity for easily cultivable pathogens (Nieman et al., 2016). However, the culturing method has several drawbacks such as a rather long incubation time, failure to identify slow-growing or obligate intracellular microorganisms, as well as pathogens other than bacteria or yeast, and an inability to detect microorganisms when the patient has previously consumed antibiotics (Gupta et al., 2023; Peker et al., 2018; Wojno et al., 2020). Meanwhile, molecular detection can't be resolved that problem. Over a long time year, molecular detection has been alternative methode for patoghen detection (Dubourg & Raoult, 2016; Váradi et al., 2017).

Therefore, the author has compiled this literature review to delve deeper into the potential and challenges of molecular diagnosis for blood infections or sepsis based on previous research findings. This literature review is expected to serve as a scholarly resource that provides an overview of improved detection techniques for diagnosing blood infections or sepsis.

METHODS

This Literature Review method was conducted using electronic databases including several databases such as Google Scholar, PubMed, and Semantic Schoolar. Articles or journals that met the inclusion and exclusion criteria (Table 1) were gathered and subsequently analyzed.

Table 1
Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Problem	National and international journals from different databases and related to the same problem formulation molecular detection in blood infections	National and international journals from different databases and related to the same problem formulation molecular detection of blood infections, but the PCR process is indirect from clinical samples
Study Desain	Cross sectional study, cohort, ekspriment study, case report, quasi eksprimen, laboratory and field research	In addition to Cross sectional study, cohort, experimental study, quasi experiment, laboratory and field research
Publication Year	2019-2023	<2019
Indexing	International journals indexed by Scopus / reputable journals or national journals indexed by Garuda	In addition to international journals indexed by Scopus / reputable journals or national journals indexed by Garuda
Journal Access	Journals that can be accessed in fulltext	Journals that are not accessible in fulltext
Language	English and Indonesian	In addition to English and Indonesian

RESULTS

In August 2023 to September 2023, the collection and selection of journals were carried out using predetermined search engines, namely Google Scholar, PubMed/NCBI, and Researchgate. The result was a total of 36,100 journals, which were then filtered based on relevant titles, resulting in 18 relevant journal titles for this research. Furthermore, further selection was conducted based on research variables.

There were 10 journals excluded as they did not meet the inclusion criteria that had been established (Table 1). The remaining 8 journals were chosen for further analysis (Table 2 and Figure 1). During the literature search using search keywords such as "PCR and bloodstream infection" and "PCR for Bloodstream infection," a total of 720 articles were found from Google Scholar, 39 articles from PubMed/NCBI, and 140 articles from Semantic Scholar

Figure 1
The process of searching literature the impact of internal quality assurance to external quality assurance result

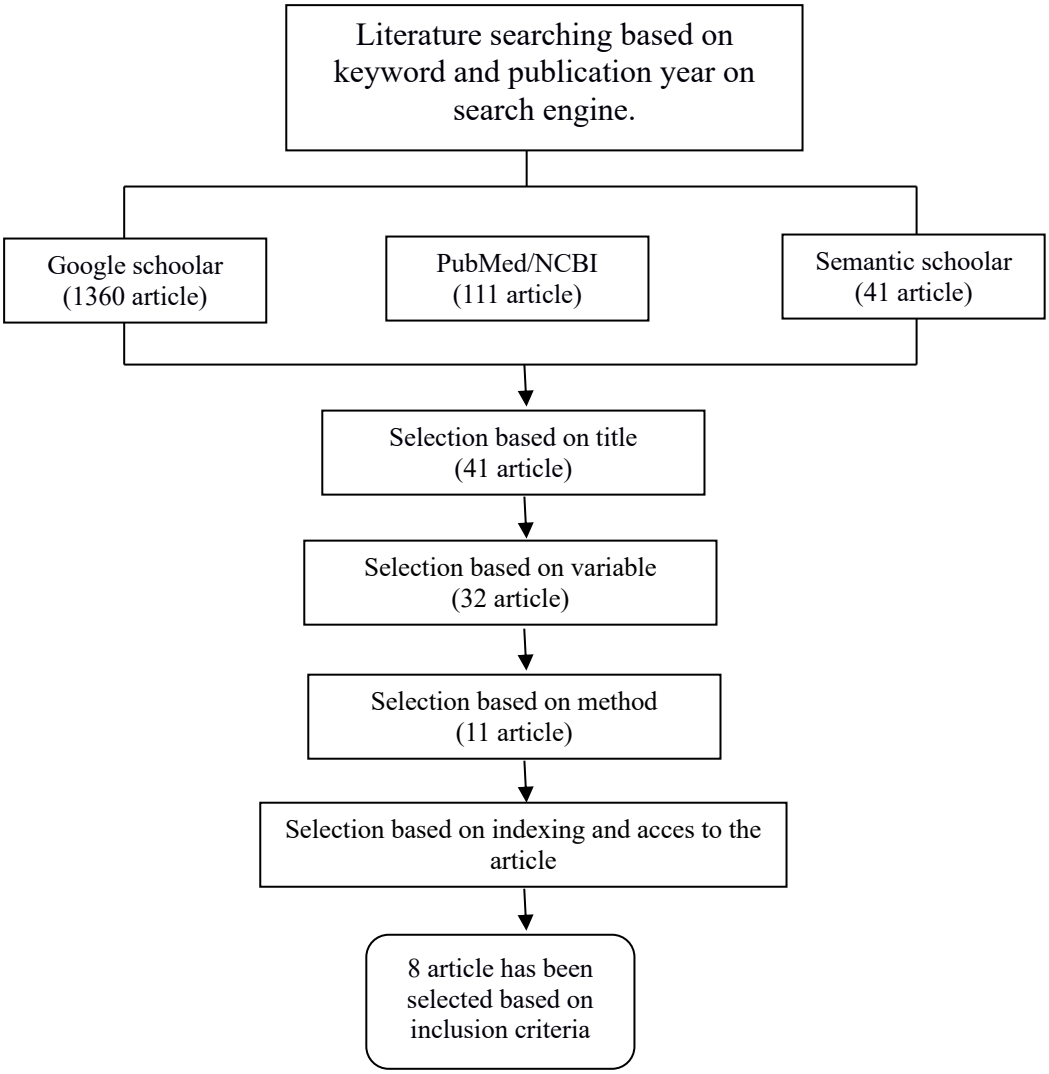

Table 2
Article List Result based on Inclusion Criteria

Title	Methode	Microorganism Test	Result	Additional Information
A diagnostic test of real-time PCR detection in the diagnosis of clinical bloodstream infection(J. Sun et al., 2022)	Total of 126 patients with bloodstream infections collected from various clinical departments of The First Hospital of Hebei Medical	17 pathogens	PCR detected a total of 43 positive samples and 83 negative samples. Five samples were positive with blood culture, and 81 were negative. The negative	-

Title	Methode	Microorganism Test	Result	Additional Information
	University. The patient's sample was divided into two parts. The one for multiplex PCR detection was performed using the Pathogeno Elite Multiplex PCR kit. Another blood culture was a fully automatic blood culture system from Autobio company.		predictive value of PCR was 0.98, with a sensitivity of 0.71 and a specificity of 0.68. A total of 38 specimens were positive for PCR but negative for blood culture, and 2 samples were positive for blood culture but negative for PCR. The top 5 pathogens with PCR detection were Epstein-Barr virus (27 cases), *Human herpes virus 5* (9 cases), *Klebsiella pneumoniae* (5 cases), *Staphylococcus* (5 cases), and *Stenotrophomonas maltophilia* (4 cases).	
Evaluation of the MagicplexTM Sepsis Real-Time Test for the Rapid Diagnosis of Bloodstream Infections in Adults (Zboromyrska et al., 2019)	809 blood samples were test used MegicplexTM and Blood culture	15 pathogens	The sensitivity and specificity of MP were 29 and 95%, respectively, while the level of agreement between BC and MP was 87%. The rate of contaminated samples was higher for BC (10%) than MP (4.8%) ($P < 0.001$). Patients with only MP-positive samples were more likely to be on antimicrobial treatment (47%) than those with only BC-positive samples (18%)	MP test could be useful in some clinical setting, such as among patients on antibiotic therapy. Nevertheless, a low sensitivity demonstrated impairs its use as a part of a routine diagnostic algorithm.
The potential utility of real-time PCR of	A total of 150 infants were		The positivity rates of blood	

Title	Methode	Microorganism Test	Result	Additional Information
the 16S-rRNA gene in the diagnosis of neonatal sepsis(İstanbullu et al., 2019)	enrolled in this prospective study. The infants were classified into two groups: sepsis group (n=100) and control group (n=50). The blood were collected for PCR and blood culture test		culture and PCR were found as 11% and 3%, respectively. The diagnosis of neonatal sepsis by PCR revealed a 16.6 % sensitivity, 97.8 % specificity, 33.3% positive predictive value and 94.8% negative predictive value compared with the blood culture.	
Candida parapsilosis bloodstream infection in an immunocompromised host with discordant multiplex polymerase chain reaction and conventional blood culture results: a case report(Jones et al., 2022)	Compared between blood culture and multiplex PCR	*Candida parapsilosis*	Conventional cultures only grew *E. Cloacae* while multiplex PCR results (BioFire® FilmArray® BCID 1) returned positive for both *Enterobacter cloacae* and *Candida parapsilosis*	The patient was give ertapenem monotherapy and defer antifungal therapy. The patient's symptoms progressed, and 11 days later, the patient was admitted with subsequent positive blood cultures for *C. parapsilosis*.
Diagnostic Performance of a Novel Multiplex PCR Assay for Candidemia among ICU Patients(Fuchs et al., 2019)	Clinical samples from 58 patients were analyzed by standard blood culture (BC) and simultaneously tested with the Fungiplex Candida PCR (FP) and the SeptiFast test (SF) for molecular detection of Candida spp	Candida	Compared to BC, the FP test showed high diagnostic power, with a sensitivity of 100% and a specificity of 94.1%. Overall diagnostic accuracy reached 94.6%. Using SF, we found a sensitivity of 60%, a specificity of 96.1%, and an overall diagnostic accuracy of 92.9%.	
Performance of real-time PCR in suspected haemodialysis catheter-related	A blood sample for rt-PCR was collected simultaneously	*Staphylococcus* spp., *Staphylococcus aureus* and *mecA*	Eighty-four paired samples were collected and compared for 40 suspected HD	Based on the rt-PCR results, antibiotics could be more appropriately

Title	Methode	Microorganism Test	Result	Additional Information
bloodstream infection: a proof-of-concept study(Acquier et al., 2023)	with each pair of blood cultures for suspected HD CRBI. The rt-PCR was performed on the whole blood, without any enrichment stage and with specific DNA primers: 16S (universal bacterial), *Staphylococcus* spp., *Staphylococcus aureus* and *mecA*		CRBI events in 37 patients. Among these, 13 (32.5%) were diagnosed as HD CRBI. All rt-PCRs except *mecA* (insufficient number of positive samples) showed high diagnostic performances within 3.5 h: 16S (sensitivity 100%, specificity 78%), *Staphylococcus* spp. (sensitivity 100%, specificity 97%), *S. aureus* (sensitivity 100%, specificity 99%).	targeted, thus cutting anti-cocci Gram-positive therapy from 77% to 29%.

DISCUSSION

Since the Covid-19 pandemic in 2020, molecular-based methods, especially PCR, have become more familiar and known to many people. This method provides quick and accurate results, thus its usage has been expanded to various other microbiological examinations, one of which is examining pathogens in the bloodstream (Maneg dkk., 2016; Zhu et al., 2020).

Generally, examinations related to blood-borne pathogens or infections usually take a considerable amount of time. Starting from blood incubation in the BAC-T Alert device to the identification of pathogenic microorganisms, it takes about 5-7 days (Sanli et al., 2016; D. Sun et al., 2021). Moreover, when patients have already undergone treatment, blood culture results tend to be low until negative (Cheng et al., 2019; Scheer et al., 2019). Moreover, previous study showed that molecular methode reduce the cost for unnecessarily treated patient (Pliakos et al., 2018; Walker et al., 2016).

This literature review describes the outcomes of several studies that evaluate PCR-based methods in diagnosing bloodstream infections. These studies involve various pathogens and patient populations, yielding varying results.

PCR-based methods, such as real-time PCR, digital PCR, and multiplex PCR, have the potential to detect various pathogens in bloodstream infections, including viruses and bacteria (Zauli, 2019). Some studies show promising results, such as the detection of

Epstein-Barr virus, Human herpes virus 5, Klebsiella pneumoniae, Staphylococcus, and Stenotrophomonas maltophilia using multiplex PCR, as well as the detection of Gram-negative pathogens using duplex dPCR (Sun, et al., 2022, Zboromyrska et al., 2019, dan Ziegler et al., 2019).

However, some limitations have also been found, such as low sensitivity in certain PCR tests, like the MagicplexTM Sepsis Real-Time Test and 16S rRNA gene PCR in neonatal sepsis (Zboromyrska et al., 2019). Additionally, discrepancies exist between multiplex PCR and blood culture in *Candida parapsilosis* bloodstream infections (Jones et al., 2022).

Study outcomes suggest that PCR-based methods can be used as an adjunct tool in specific clinical settings, especially for patients undergoing antibiotic therapy. However, these methods should ideally be used in conjunction with other diagnostic methods, such as blood culture, to enhance diagnostic accuracy and treatment. AlQahtani a stated that the combination of diagnosis using PCR to identify blood cultures significantly shortened the time to optimal antimicrobial therapy by 1.7 days (AlQahtani et al., 2021). The sensitivity and specificity of PCR-based methods may vary depending on the pathogen and patient population (McCarthy & Walsh, 2016; Tkadlec et al., 2019). The choice of PCR tests and result interpretation should be based on clinical context and available evidence.

Studies on the MagicplexTM Sepsis Real-Time Test indicate that despite its usefulness in some clinical settings, its low sensitivity hinders its use as part of routine diagnostic algorithms. Studies on 16S rRNA gene PCR suggest that including all susceptible microorganisms in PCR tests can increase its sensitivity. Studies on duplex dPCR show that this method has good sensitivity in detecting Gram-negative pathogens in patients' blood. Further research is necessary to validate the performance of PCR-based methods in various patient populations and pathogens. Additionally, it's crucial to optimize the platforms and PCR tests used. The implementation of PCR-based methods in clinical practice should consider cost-effectiveness, turnaround time, and impact on patient outcomes. Thus, although PCR-based methods offer the potential to enhance the diagnosis of bloodstream infections, their use should be carefully considered within the appropriate clinical context and by taking into account the existing limitations.

CONCLUSION

Examination of pathogens causing bloodstream infections using PCR methods holds promising potential for the future. However, research on the limitations of the method and optimization of PCR methods for

detecting pathogens in the blood needs further investigation.

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