INPLASY

Evaluation of Serum Procalcitonin in the Differentiation between Gram-Negative and Gram-Positive Bacterial Infections in Adults with Sepsis or Bacteremia: A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 June 2025 and was last updated on 19 June 2025.

INTRODUCTION

Review question / Objective "In adult patients with confirmed sepsis or bacteremia, what is the ability of serum procalcitonin levels to differentiate infections caused by Gram-negative bacteria, Gram-positive bacteria, and fungi, considering its diagnostic performance?"

Rationale Sepsis and bacteremia are severe clinical conditions associated with high rates of morbidity and mortality, requiring rapid diagnosis and appropriate, early antimicrobial therapy. The initial choice of antimicrobial treatment is often empirical, based on clinical suspicion of the infection site, patient risk factors, and local epidemiology. However, the precise identification of the etiological agent—whether it is a Gram-negative bacterium, a Gram-positive bacterium, or a fungus—is crucial for optimizing therapy, improving clinical outcomes, and combating the progression of antimicrobial resistance. Traditional microbiological methods, such as cultures, while being the gold standard, are time-consuming, which can delay the start of targeted treatment.
Procalcitonin (PCT) is a biomarker that is widely studied and used in clinical practice, mainly to aid in the diagnosis of bacterial infections and to guide antibiotic therapy, especially in respiratory tract infections and in critically ill patients. It is known that its levels rise more sharply in bacterial infections than in viral infections or non-infectious inflammatory conditions. There is growing investigation into whether PCT levels could also provide information about the type of pathogen causing the infection. Some studies suggest that infections by Gram-negative bacteria tend to induce a more robust inflammatory response, with the release of endotoxins (like lipopolysaccharide - LPS), resulting in higher PCT levels compared to infections by Gram-positive bacteria. Likewise, invasive fungal infections may present distinct PCT profiles from bacterial ones. Many existing reviews have focused on the distinction between bacterial and non-bacterial infections, or on its utility for antibiotic de-escalation, but a direct comparison of PCT levels among these three specific pathogen

groups in the context of a confirmed severe infection remains an area that would benefit from a robust synthesis of the evidence.

Condition being studied Based on the provided text, the conditions being studied are:

Sepsis and Bacteremia: The study population consists of adult patients with a confirmed diagnosis of sepsis or bacteremia. These are described as severe clinical conditions that require rapid diagnosis and treatment.

The research aims to differentiate the underlying cause of these conditions by analyzing infections caused by three specific groups of pathogens:

Gram-negative bacteria (GNB)
Gram-positive bacteria (GPB)
Fungi.

METHODS

Search strategy Based on the document provided, the search strategy is as follows:

The search strategy is designed to be exhaustive, utilizing multiple electronic databases to maximize the retrieval of relevant studies.

4.1. Databases
Searches will be conducted in the following bibliographic databases:

Embase
PubMed (including MEDLINE)
LILACS (Latin American and Caribbean Health Sciences Literature)
Scopus
Web of Science
CINAHL (Cumulative Index to Nursing and Allied Health Literature)
Google Scholar will be used to identify grey literature, with a focus on the most relevant initial results.
4.2. Search Terms
The search terms will be built using a combination of controlled descriptors (like MeSH for PubMed and Emtree for Embase) and free-text terms, combined with Boolean operators (AND, OR). The strategy will be adapted for each database, but it will be centered around the following core terms:

Main terms: "procalcitonin" AND “Gram-Positive Bacteria" AND “Gram-Negative Bacteria” OR "fungi" AND “Sepsis” OR “Bacteremia”.

Sample PubMed/MeSH string: (("procalcitonin"[MeSH Terms] OR "procalcitonin"[All Fields]) AND ("Gram-Positive Bacteria"[All Fields] OR "Gram-Positive Bacteria"[MeSH Terms]) AND ("Gram-Negative Bacteria"[All Fields] OR "Gram-Negative Bacteria"[MeSH Terms]) OR ("fungi"[All Fields] OR "fungi"[MeSH Terms]) AND ("Sepsis"[All Fields] OR "Sepsis"[MeSH Terms]) OR ("Bacteremia"[All Fields] OR "Bacteremia"[MeSH Terms])) AND ("2015/06/01"[PDat] : "2025/12/30"[PDat]).
The entire search process, including the date of each search, the number of results, and the exact strings used, will be detailed.

4.3. Manual Search
In addition to database searches, a manual search of the reference lists of included articles and relevant reviews will be performed to find any studies missed by the electronic search.

Participant or population Based on the research protocol provided, the patient population to be addressed in the review is defined by the following eligibility criteria:

Inclusion Criteria:

Population: The review will include studies focusing on adult patients, defined as being 18 years of age or older.
Diagnosis: These patients must have a confirmed diagnosis of either sepsis or bacteremia.
Microbiological Confirmation: The studies must have microbiological confirmation of the causative pathogen and present data stratified by the type of pathogen (Gram-negative bacteria, Gram-positive bacteria, or fungi).

Exclusion Criteria:

Studies involving pediatric populations (patients under 18 years old) will be excluded.
Studies involving patients with co-infections that are not stratified by the specific etiological agent will also be excluded.

Intervention Based on the provided research protocol, the intervention to be evaluated is a diagnostic test, not a therapeutic treatment.

The specific intervention is the evaluation of serum procalcitonin (PCT) levels.

The review aims to assess the capacity of these serum PCT levels to differentiate between infections caused by Gram-negative bacteria,

Gram-positive bacteria, and fungi in adult patients with confirmed sepsis or bacteremia.

Comparator Based on the research protocol, this review does not evaluate a comparative intervention in the traditional sense (like a placebo or an alternative treatment). Instead, the "comparison" refers to the different groups of patients whose procalcitonin (PCT) levels are being compared to assess the test's diagnostic accuracy.
The comparative groups are patients with confirmed sepsis or bacteremia caused by different etiological agents. The review will include studies that compare or provide stratified data on serum PCT levels in infections caused by:
Gram-negative bacteria (GNB)
Gram-positive bacteria (GPB)
Fungi.

Study designs to be included Based on the research protocol, the review will specifically include clinical observational studies. The eligible study designs are:Cohort studies Case-control studies Cross-sectional studies.

Eligibility criteria Based on the research protocol, the following additional inclusion and exclusion criteria are defined outside of the core PICOS framework:

Additional Inclusion Criteria
Publication Period: The review will only include articles published within a 10-year timeframe, specifically between June 2015 and December 2025.
Language: Included articles must be published in either English or Portuguese.
Additional Exclusion Criteria
Publication Type: Certain types of publications will be excluded, including:

Case reports, editorials, letters to the editor, and conference abstracts.
Literature reviews, meta-analyses, and guidelines.
Data Sufficiency: Studies with insufficient data for the extraction or statistical conversion of procalcitonin levels by pathogen type will be excluded.
Study Subjects: Animal or in vitro studies are excluded.

Information sources Based on the research protocol provided, the intended information sources for the review include electronic databases, grey literature, and manual searches.

The specific sources are:

Electronic Databases: The primary search will be conducted across several bibliographic databases. These include:
Embase
PubMed (including MEDLINE)
LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde)
Scopus
Web of Science
CINAHL (Cumulative Index to Nursing and Allied Health Literature)
Grey Literature: Google Scholar will be searched to identify relevant grey literature and to ensure the comprehensiveness of the search.

Manual Searches: A manual search will be performed on the reference lists of all articles included in the review, as well as on the references of other relevant reviews and meta-analyses found during the search process. This is done to identify any additional studies that the electronic search may have missed.

Main outcome(s) The review will focus on two main categories of outcomes related to the performance of serum procalcitonin (PCT).
The timing of PCT measurement is not specified as a fixed outcome, but rather the data will be extracted as reported in the included studies.

The outcomes are:
1. Quantitative Procalcitonin Levels
The review will extract and synthesize the reported serum PCT levels for each pathogen group. The specific data points to be collected include:

Mean or median PCT levels.
Measures of dispersion, such as standard deviation, interquartile range (IQR), or percentiles.
These quantitative levels will be analyzed separately for infections caused by Gram-negative bacteria (GNB), Gram-positive bacteria (GPB), and fungi.

2. Diagnostic Accuracy Measures
The review will compile and analyze the diagnostic performance of PCT in differentiating between the specified pathogen groups. The effect measures to be extracted include:
Sensitivity and specificity.
Positive and negative predictive values.
Likelihood ratios.
The Area Under the Curve (AUC) from the Receiver Operating Characteristic (ROC) curve, along with its corresponding confidence intervals.
The specific PCT cutoff points used in the studies to perform the differentiations between pathogen groups.

Data management Based on the research protocol, the following mechanisms will be used to manage records and data throughout the review process:

Management of Study Records (Selection Process)
The process of managing the study records from the initial search to final inclusion is systematic and designed to minimize bias.

Reference Management Software: After the initial database search, a reference management software (Mendeley) will be used to remove duplicate records.
Two-Phase Independent Screening: The selection process will be conducted in two phases by two independent researchers to ensure impartiality.
Title and Abstract Screening: Initially, the two researchers will screen all unique records by title and abstract to pre-select potentially relevant articles.
Full-Text Reading: The full texts of the pre-selected articles will then be read by both researchers to determine their final eligibility based on the inclusion and exclusion criteria.
Conflict Resolution: Any disagreements between the two researchers at any stage will be resolved through discussion to reach a consensus. If a consensus cannot be reached, a third supervising researcher will mediate and make the final decision.
Documentation: A detailed PRISMA flowchart will be used to document the entire selection process, showing the number of records identified, screened, assessed for eligibility, and included in the final review, with reasons for exclusion.
Management of Extracted Data
The data extracted from the final included studies will be managed with similar rigor.

Standardized Data Extraction Form: A pre-defined, standardized form will be used for data extraction to ensure consistency and minimize errors. This form will include fields for study characteristics, population details, PCT methodology, quantitative PCT levels, and diagnostic accuracy measures.

Independent Data Extraction: Data extraction will be performed independently by two researchers.
Conflict Resolution: Similar to the selection process, any discrepancies in the extracted data between the two researchers will be resolved through discussion and consensus, with a third researcher consulted if necessary.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of each included study will be assessed independently by two researchers.

Assessment Tool
The Newcastle-Ottawa Scale (NOS) will be the tool used to assess the risk of bias in the included observational studies.
The NOS evaluates three primary dimensions of a study: patient selection, the comparability between the groups, and the assessment of the outcome. It assigns a score that reflects the overall quality of the study.
Assessment Process
Two independent researchers will apply the NOS to every included study.
The scores and the justifications for each item on the scale will be recorded.
Any disagreements that arise between the two researchers during the assessment will be resolved through discussion or, if consensus cannot be reached, by consulting a third researcher.
Impact on Synthesis
The results from the quality assessment will be integrated into the final review in several ways:

The results of the risk of bias assessment will be presented in tables and discussed within the review.
Studies identified as having a high risk of bias will have their conclusions interpreted with caution, and their impact on the overall strength of the evidence will be considered.
If heterogeneity among studies is very high, a sensitivity analysis that excludes low-quality studies may be considered.
Fontes.

Strategy of data synthesis The data will be analyzed through a qualitative and narrative synthesis, and a statistical meta-analysis will not be performed. The objective is to integrate the findings from the individual studies in a coherent and comprehensive manner to address the review's specific aims. The analysis will involve the following steps: Data Presentation The extracted data will be organized and presented clearly using a combination of formats: Tables: To summarize the general characteristics of the included studies, the reported procalcitonin (PCT) levels for each pathogen group (Gram-negative bacteria, Gram-positive bacteria, and fungi), and the diagnostic accuracy parameters (e.g., sensitivity, specificity, AUC). Figures: Visual aids such as bar graphs or scatter plots may be used to illustrate the distribution of PCT levels across the different pathogen groups. Descriptive forest plots (without statistical pooling) may also be used to visualize the diagnostic accuracy results from each study.

Narrative Description: A detailed textual summary will be provided to discuss the main findings, compare results across studies, and describe observed patterns and trends. Analytical Approach The narrative synthesis will specifically address the review's objectives: Analysis of PCT Levels: The mean or median PCT levels for Gram-negative bacteria (GNB), Gram-positive bacteria (GPB), and fungi will be compiled and presented. The analysis will describe the variability in these values and discuss whether the data supports a hierarchical pattern (e.g., GNB > GPB > Fungi). Analysis of Diagnostic Accuracy: The reported accuracy parameters (sensitivity, specificity, AUC, etc.) for differentiating between the pathogen groups will be compiled and critically discussed. Special attention will be given to the variability in the PCT cutoff points used across studies and how these impact the accuracy results. Analysis of Heterogeneity: There will be an in-depth discussion of the potential sources of heterogeneity between studies. This analysis will explore how factors such as patient population characteristics (e.g., comorbidities like renal function, sepsis severity, primary site of infection), PCT measurement methods, and study design might explain the variation seen in the results. Summary of Clinical Utility: The analysis will culminate in a summary of the evidence regarding the clinical utility of PCT as a tool for early etiological differentiation in sepsis and bacteremia. This will include highlighting the strengths and limitations of the biomarker for this purpose and identifying any gaps in the existing literature.

Subgroup analysis The plan is to conduct an in-depth discussion exploring how the following factors may explain variability in procalcitonin (PCT) levels and diagnostic accuracy parameters among the included studies:
Patient Population Characteristics:
Comorbidities, with a specific focus on renal function.
The severity of sepsis, as measured by scoring systems like SOFA or APACHE II.
The primary site of the infection.
Methodological Characteristics:

Different PCT cutoff points used across the studies.
The specific methodologies used for PCT measurement.
The different study designs (e.g., cohort, case-control).

Sensitivity analysis The protocol states that a sensitivity analysis involving the exclusion of low-quality studies may be considered if the heterogeneity among the included studies is found to be very high.

Country(ies) involved Brazil.

Keywords Procalcitonin; Sepsis; Bacteremia; Gram-Negative Bacteria; Gram-Positive Bacteria; Fungal Infections; Diagnostic Accuracy; Systematic Review; Biomarkers.

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