INPLASY

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

INPLASY202560086

doi: 10.37766/inplasy2025.6.0086

Received: 19 June 2025

Published: 19 June 2025

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ADMINISTRATIVE INFORMATION

Support - None.

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

Review Stage on June 13, 2026 - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202560086

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 13 June 2026.

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 The search is structured in three conceptual blocks combined with AND, with synonyms combined with OR within each block: (1) procalcitonin; (2) pathogen (Gram-negative OR Gram-positive OR fungi); (3) condition (sepsis OR bacteremia OR bloodstream infection). Because "procalcitonin" is not a primary MeSH term (it is a Supplementary Concept), free-text searching is mandatory in all databases. Fully validated, database-specific strings were developed for PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, LILACS/BVS and Google Scholar, and are reported in full in accordance with PRISMA-S. Publication window: 01 June 2015 to 31 December 2025; languages: English and Portuguese.

Participant or population Adults (≥18 years) with sepsis or bacteremia. Sepsis is defined by the Sepsis-3 criteria (organ dysfunction due to a dysregulated host response to infection) for studies published from 2016 onward; for earlier studies, the definition used (SIRS/Sepsis-2) is recorded as a heterogeneity variable. Bacteremia is defined as at least one blood culture positive for a clinically significant pathogen. Studies must provide pathogen-stratified data (Gram-negative bacteria, Gram-positive bacteria, or fungi). Pediatric patients (<18 years) and non-stratified co-infections are 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 This is a diagnostic test accuracy (DTA) systematic review; eligibility is framed using the PIRD structure (Population, Index test, Reference standard, Target condition), with study design as an additional criterion. The reference standard is microbiological identification of the pathogen by culture (blood culture for bacteremia; sterile-site culture where applicable); the imperfection of culture (false negatives under prior antibiotics, contamination, fastidious fungi) is addressed in the risk-of-bias assessment.

Inclusion criteria: clinical observational studies (cohort, case-control, cross-sectional) reporting quantitative procalcitonin data (mean/median and a measure of dispersion) and/or diagnostic accuracy data (sensitivity, specificity, predictive values, likelihood ratios, AUC) stratified by pathogen group (Gram-negative bacteria, Gram-

positive bacteria, fungi); published between June 2015 and December 2025; in English or Portuguese.

Exclusion criteria: populations under 18 years; case reports, editorials, letters to the editor, conference abstracts, narrative and systematic reviews, meta-analyses and guidelines; insufficient procalcitonin data by pathogen type for extraction or statistical conversion; co-infections not stratified by etiological agent; animal or in vitro studies.

The restriction to English and Portuguese is a feasibility decision for this undergraduate thesis; it is declared as a limitation, and studies excluded solely on the basis of language are counted in the PRISMA-DTA flow diagram.

Information sources Primary electronic databases: Embase, PubMed/MEDLINE, LILACS, Scopus, Web of Science and CINAHL. Complementary sources: Google Scholar (grey literature). Manual searching of the reference lists of included studies and of relevant reviews. Each search is dated and archived with the number of results retrieved.

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 Records are managed in a reference manager (Zotero or Mendeley) for de-duplication, and screening is performed in Rayyan. After duplicate removal, two reviewers independently screen titles/abstracts and then full texts; disagreements are resolved by consensus or a third reviewer. Data are extracted independently and in duplicate using a standardized form, with cross-checking of numerical values. The selection process is documented in a PRISMA-DTA flow diagram.

Quality assessment / Risk of bias analysis Risk of bias is assessed independently by two reviewers (disagreements resolved by consensus or a third reviewer). For the diagnostic accuracy component, QUADAS-2 is applied with per-domain judgement (patient selection; index test; reference standard; flow and timing) and a separate applicability assessment; no summative numeric score is computed. QUADAS-C is added only if procalcitonin is formally compared with another index test (e.g., CRP or IL-6) in the same patients. For the procalcitonin-level component (continuous measure across pathogen groups), ROBINS-E is used, treating pathogen type as the exposure. Results are displayed as robvis traffic-light plots. This supersedes the Newcastle-Ottawa Scale stated in the original protocol.

Strategy of data synthesis The primary synthesis is a structured narrative following the SWiM guideline, organised by objective, with tabulated study characteristics, PCT levels per pathogen group and accuracy parameters, plus descriptive forest plots. Meta-analysis is performed only when a sufficient number of clinically and methodologically comparable studies is available; in that case, diagnostic accuracy is modelled using bivariate random-effects or HSROC models (accounting for threshold effects), and PCT levels are pooled as mean differences (or standardised mean differences), converting median/IQR to mean/SD using the Wan and Luo methods. Heterogeneity is described and, where pooling occurs, quantified by I^2. Publication bias is assessed with the Deeks asymmetry test (appropriate for diagnostic accuracy), only when ≥10 studies per comparison; funnel plots and Egger's test are not used for the accuracy component. Certainty of evidence is graded with

GRADE adapted for diagnostic tests (Summary of Findings table) for the accuracy component and standard GRADE for the continuous-level component. This supersedes the original statement that no meta-analysis would be performed.

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 Pre-specified sensitivity analyses, when the number of studies allows: exclusion of studies at high risk of bias by QUADAS-2; stratification by PCT cutoff; stratification by study design; and separate analysis by the sepsis criterion used (Sepsis-3 vs earlier definitions). Analyses based on "double-blinding" or "placebo" do not apply to observational accuracy studies and are not used.

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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