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# Systematic review and meta-analysis of the diagnostic value of four biomarkers in detecting neonatal sepsis in low- and middle-income countries

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## ABSTRACT

**Background** Biomarkers may enhance diagnostic capability for common paediatric infections, especially in low- and middle-income countries (LMICs) where standard diagnostic modalities are frequently unavailable, but disease burden is high. A comprehensive understanding of the diagnostic capability of commonly available biomarkers for neonatal sepsis in LMICs is lacking. Our objective was to systematically review evidence on biomarkers to understand their diagnostic performance for neonatal sepsis in LMICs.

**Methods** We conducted a systematic review and meta-analysis of studies published in English, Spanish, French, German, Dutch, and Arabic reporting the diagnostic performance of C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC) and procalcitonin (PCT) for neonatal sepsis. We calculated pooled test characteristics and the area under the curve (AUC) for each biomarker compared with the reference standards blood culture or clinical sepsis defined by each article.

**Results** Of 6570 studies related to biomarkers in children, 134 met inclusion criteria and included 23 179 neonates. There were 80 (59.7%) studies conducted in LMICs. CRP of ≥60 mg/L (AUC 0.87, 95% CI 0.76 to 0.91) among 1339 neonates and PCT of ≥0.5 ng/mL (AUC 0.87, 95% CI 0.70 to 0.92) among 617 neonates demonstrated the greatest discriminatory value for the diagnosis of neonatal sepsis using blood culture as the reference standard in LMICs.

**Conclusions** PCT and CRP had good discriminatory value for neonatal sepsis in LMICs. ESR and WBC demonstrated poor discrimination for neonatal sepsis in LMICs. Future studies may incorporate biomarkers into clinical evaluation in LMICs to diagnose neonatal sepsis more accurately.

**PROSPERO registration number** CRD42020188680.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite decreasing incidence over time, bacterial infections contribute significantly to neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries (LMICs).
⇒ In many LMICs, reference standard diagnostics for bacterial infections such as blood cultures are often unavailable.
⇒ C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and procalcitonin (PCT) have been incorporated into clinical predictive algorithms in high-income countries but their discriminatory value in LMICs is less clear.

### WHAT THIS STUDY ADDS

⇒ In a systematic review and meta-analysis including 134 studies and 23 179 neonates, none of the evaluated biomarkers had sufficient specificity or discriminatory value to be used in isolation to diagnose neonatal sepsis in LMICs.
⇒ CRP and PCT had good discriminatory value for neonatal sepsis in LMICs.
⇒ ESR and WBC had poor discriminatory value for neonatal sepsis in LMICs.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ CRP, ESR, WBC, and PCT alone should not be used to differentiate neonates at risk for neonatal sepsis.
⇒ Future studies may incorporate biomarkers into clinical evaluation in LMICs to diagnose neonatal sepsis more accurately.

## INTRODUCTION

Despite decreasing incidence over time, bacterial infections contribute significantly to childhood morbidity and mortality worldwide, particularly in low- and middle-income countries (LMICs).[1 2] Neonatal sepsis is a common cause of neonatal morbidity and mortality in LMICs.[1] Nonetheless, there is no unified criteria for the diagnosis of neonatal sepsis, which makes clinicians in resource-limited settings with scarce access to blood cultures rely on a clinical diagnosis.

In sub-Saharan Africa, as many as 22%–25% of determined causes of fever are bacterial in nature among children presenting for clinical care.[3 4] However, in many LMICs, reference

standard diagnostics for bacterial infections such as blood cultures, chest radiography, or polymerase chain reaction (PCR) are often unavailable.[5–7] This may result in widespread overuse of antibiotics, or, conversely, under-recognition and undertreatment of bacterial infections.

Biomarkers (or biological markers) are objective measures that may be evaluated as indicators of pathological processes and have the potential to facilitate risk stratification for infectious diseases.[8] C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and procalcitonin (PCT) have been incorporated into clinical predictive algorithms in high-income countries (HICs).[9 10] However, biomarkers are not yet widely used in many LMICs where there is greater burden of bacterial disease and lower rates of immunisation. Consequently, an understanding of how biomarkers perform among children in these settings is lacking.

A reliable approach to identifying a child's risk of infection may enhance the quality of clinical care, promote better resource utilisation, and allow for targeted and responsible antibiotic use in settings with limited access to reference standard diagnostics. A comprehensive understanding of the diagnostic capability of commonly available biomarkers for neonatal sepsis in LMICs is lacking but may allow for more accurate diagnoses among neonates and more judicious antibiotic use. Our objective was to systematically review existing evidence on the use of four biomarkers (CRP, ESR, WBC, and PCT) to understand their diagnostic performance against the reference standards of blood culture and clinical sepsis for neonatal sepsis, with a focus on studies conducted in LMICs. We focused our analysis on neonatal sepsis as it makes significant contributions to childhood morbidity and mortality globally.[1 2]

## METHODS

### Study design

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] We registered this study in PROSPERO, an international prospective register for systematic reviews (CRD42020188680).

We focused our review on CRP, ESR, WBC, and PCT to understand the potential use of these biomarkers in clinical settings in which reference standard diagnostic testing may be limited. Though other biomarkers, including proadrenomedullin and various serum interleukins, have also been used to assess the presence of bacterial illness against reference standards,[12 13] these are not currently routinely accessible in many settings, both in HICs and particularly in LMICs, so were excluded from the analysis.

### Patient and public involvement statement

The development of the research question was informed by the high disease burden of neonatal sepsis. Patients were not involved in the design, recruitment, or conduct of the study, nor were they advisers in this study. Results of this study have been made publicly available through publication.

### Data sources

We searched the Medline, EMBASE, DARE, CINAHL, and Babelmesh databases on 12 February 2021 and conducted an updated search on 29 August 2022. We extracted articles that were included in each of these databases from their inception to 29 August 2022. The search terms used to identify studies that focused on the use of the four biomarkers of interest are included in online supplemental appendix 1. Our search was limited to articles published in English, Spanish, French, German, Dutch, and Arabic as members of our team were fluent in these languages.

### Inclusion and exclusion criteria

We included studies that met the following criteria (1) were peer-reviewed, original research articles published from the inception of each database to 29 August 2022, (2) evaluated the use of one of the four biomarkers of interest in the diagnosis of an infectious disease, (3) included participants aged 0–18 years and (4) included a control group that did not test positive with a reference standard as a comparison for the diagnostic performance of the biomarkers evaluated. Initially, our search was not restricted to specific diseases. However, *post hoc*, we decided to focus our analysis on neonatal sepsis as there were at least 20 studies that met our inclusion criteria, and it contributes to a large burden of childhood morbidity and mortality globally. There were >20 studies that reported the test characteristics of the included biomarkers for pneumonia. However, these were not included in our manuscript because those studies did not differentiate viral from bacterial disease.

We excluded studies that met any of the following criteria: (1) articles that were not published in English, Spanish, French, German, Dutch, or Arabic, (2) abstracts without full text, (3) articles that only included highly medicalised populations, (4) articles reporting only mean or median values for biomarkers, (5) articles that did not evaluate children separately if adults aged >18 years were included, (6) articles that only assessed changes in biomarkers during treatment, and (7) case reports, editorials, study protocols, review articles, systematic reviews, and meta-analyses. We reviewed systematic reviews and meta-analyses for other articles reporting primary data our initial query did not capture. Any potential articles identified therein were included if they met inclusion criteria.

### Definitions

We used the definitions used for our outcome of neonatal sepsis as reported in the included studies (ie, either positive blood culture or clinical sepsis).[14] Study countries

were defined as low- middle-income and high-income according to the World Bank definitions.[15]

### Data extraction and risk of bias assessment

Using the results from our database query, we uploaded all articles into the platform Covidence (Melbourne, Australia) to screen article titles and abstracts for potential inclusion. Two reviewers independently screened articles in two rounds. Each reviewer was blinded to the other reviewer's screening. The first round included a review of all abstracts for the presence of exclusion criteria. All article titles and abstracts that resulted in disagreement between two independent reviewers were reviewed by an arbiter (CAR) to assess inclusion or exclusion. The second round included a review of article full texts for those remaining after titles and abstracts were reviewed. The full text of articles in Spanish, French, German, Dutch, or Arabic were screened and reviewed by a team member who was fluent in the respective language.

We reviewed the full text of each article that was included after the initial phase of article title and abstract review. We extracted the following information from each included article: study location (eg, outpatient, emergency department, inpatient such as neonatal intensive care unit), study design, study country, included patient ages, disease studied, biomarker(s) evaluated, reference standard and study inclusion and exclusion criteria. Biomarkers were considered diagnostic if they were used to distinguish an infection in a child from healthy controls or children who had negative reference standard testing. We extracted the reported number of true negatives (TNs), true positives (TPs), false negatives (FNs), and false positives (FPs) based on reported biomarker cut points and reference standard testing. For studies that did not report these numbers, we extracted the reported sensitivity, specificity, positive and negative likelihood ratios wherever possible and emailed the corresponding author to request additional data. If there was no answer to an initial email request, a second email was sent 2 weeks later.

The risk of bias of the included studies was assessed using the Quality Assessment of Studies for Diagnostic Accuracy Included in Systematic Reviews-2 (QUADAS-2) tool, which is designed to assess bias and applicability concerns for diagnostic studies.[16]

### Statistical analyses

If a study did not provide the TN, TP, FN, and FP but provided sensitivity, specificity, and the total population number, and corresponding authors did not respond to our request, we calculated the 2×2 table numbers rounded to the nearest integer. We reported the aggregate performance of each biomarker cut point with up to two reference standards in the same studies (eg, blood culture or clinical sepsis) for neonatal sepsis and alone in cases in which ≥3 studies reported the same cut point.

Many of the studies that met our inclusion criteria used different cut points for their respective biomarker. We evaluated each biomarker cut point used by ≥3 studies individually using a bivariate model created by Reitsma *et al* through the reitsma function in the R package Mada.[17 18] The bivariate analysis method created by Reitsma *et al* produces summary estimates of sensitivity and specificity that include 95% CIs that account for heterogeneity. We also calculated Holling's sample size adjusted measure for heterogeneity ($I^2$) which was developed for use in bivariate meta-analyses of diagnostic accuracy.[19] We calculated the sensitivity, specificity, and the area under the curve (AUC) along with their respective 95% CIs, for each disease and biomarker combination. 95% CIs for AUCs were calculated through bootstrapping with 2000 resamplings via the AUC boot function in the dmetatools R package created by Noma H.[20] We calculated and reported the highest Youden's index for each biomarker and disease combination. Based on published standards, we used the following scale to qualify the discriminatory value of each score: AUC ≥0.90 for 'excellent discrimination', AUC 0.80–0.89 for 'good discrimination', AUC 0.70–0.79 for 'minimal discrimination', and 'poor discrimination' for AUC <0.70.[21–23] We subanalysed all results by study country income group according to the World Bank and reference standard if there were ≥3 studies using the same cut point within that subgroup. All statistical analyses were conducted using SAS V.9.4 and R V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Study selection and characteristics

There were 6570 studies identified through our search. After abstract screening, 1816 full-text articles were reviewed and 134 reported biomarker performance for neonatal sepsis and met our inclusion criteria (figure 1). In the 134 studies included in the pooled analysis, there were 23 179 total neonates. The 134 studies reported work conducted in 42 different countries, 80 (59.7%) in LMICs, and 54 (40.3%) in HICs.

Included study characteristics are described in online supplemental table 1. Of the 134 included studies, 70 (52.2%) were deemed low risk for bias (QUADAS-2 of 1 or 2), 43 (32.1%) were deemed intermediate risk (QUADAS-2 of 3), and the remaining 21 (15.7%) had high risk of bias (QUADAS-2 of 4 or 5). Of the 80 studies conducted in LMICs, 36 (45.0%) were low risk for bias, 29 (36.3%) were intermediate risk, and the remaining 15 (18.8%) had high risk of bias. Following a similar distribution, of the 54 studies conducted in HICs, 34 (63.0%) were low risk for bias, 14 (25.9%) were intermediate risk, and the remaining 6 (11.1%) had high risk of bias.

### Biomarker performance

Of the 134 studies that evaluated the performance of biomarkers for neonatal sepsis, 109 (81.3%) evaluated CRP, 3 (2.2%) evaluated ESR, 17 (12.7%) evaluated WBC, and 31 (23.1%) evaluated PCT. Of the 134 studies,

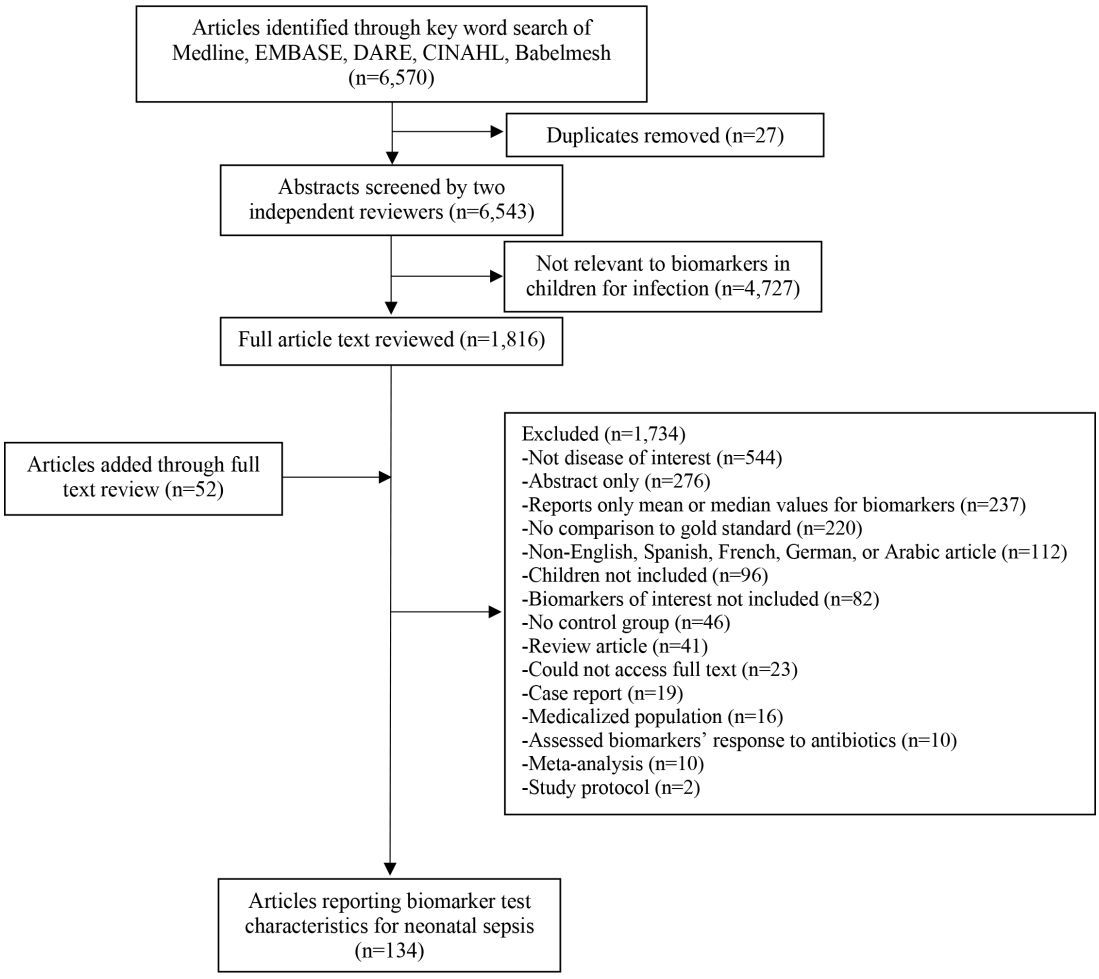


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing the identification, screening and inclusion of studies for the use of biomarkers in the diagnosis of infections in children.

123 (91.8%) used blood culture as the reference standard and 11 (8.2%) used clinical sepsis.

The CRP cut point with the highest Youden's index in the diagnosis of neonatal sepsis in LMICs was ≥60 mg/L using blood culture as the reference standard among 1339 neonates from nine studies (table 1). A CRP of ≥60 mg/L demonstrated good discriminatory value in differentiating neonates at risk of neonatal sepsis (AUC 0.87, 95% CI 0.76 to 0.91). Among studies conducted in all settings, the CRP cut point that demonstrated the highest Youden's index was ≥2.5 mg/L with blood culture as the reference standard among 263 neonates and had good discriminatory value (AUC 0.83, 95% CI 0.70 to 0.93) among three studies.

ESR was evaluated less commonly than CRP for the diagnosis of neonatal sepsis in the included studies. Among 3 studies with 599 neonates in all country brackets using blood culture as the reference standard, an ESR of ≥15 mm/hour had a low Youden's index (0.11) and poor discriminatory value (AUC 0.36, 95% CI 0.17 to 0.85) (online supplemental table 2). There were not enough studies to evaluate ESR for the diagnosis of neonatal sepsis in HICs or LMICs alone. WBC was the biomarker with the lowest sensitivity and specificity among biomarkers for the diagnosis of neonatal sepsis in all study settings (online supplemental table 3).

The PCT cut point with the highest sensitivity and specificity was ≥2.0 ng/mL using blood culture and clinical sepsis as the reference standard for neonatal sepsis among 728 neonates from eight studies conducted in LMICs (Youden's index 0.55) (table 2). A PCT of ≥0.5 ng/mL demonstrated good discriminatory value in diagnosing neonatal sepsis (AUC 0.87, 95% CI 0.70 to 0.92). Among studies conducted in all settings, a PCT of ≥1.7 ng/mL demonstrated the highest sensitivity and specificity (Youden's index 0.52) among 433 neonates from three studies and had good discriminatory value (AUC 0.83, 95% CI 0.71 to 0.88).

## DISCUSSION

In this systematic review and meta-analysis including 134 studies and over 23 000 neonates, the utility of CRP, ESR, WBC, and PCT demonstrated substantial heterogeneity in the diagnosis of neonatal sepsis. CRP and PCT had good discriminatory value for neonatal sepsis in LMICs. However, none of the evaluated biomarkers had sufficient specificity or discriminatory value to be used in isolation

**Table 1** Test characteristics of C reactive protein (CRP) in the diagnosis of neonatal sepsis

| CRP cut point (mg/L), ≥ | Sensitivity (95% CI) | Specificity (95% CI) | Youden's index | Area under the curve | Reference standard(s) | Total Patients, n | Disease, n* | Studies, n | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| All included studies | | | | | | | | | |
| 6 | 0.76 (0.69 to 0.81) | 0.77 (0.69 to 0.83) | 0.53 | 0.83 (0.76, 0.85) | Blood culture and clinical sepsis | 2910 | 1122 | 24 | 2.9–4.2 |
| 10 | 0.68 (0.61 to 0.74) | 0.81 (0.76 to 0.86) | 0.49 | 0.80 (0.73, 0.82) | Blood culture and clinical sepsis | 8243 | 1829 | 38 | 8.2–10.9 |
| 60 | 0.78 (0.67 to 0.86) | 0.80 (0.66 to 0.89) | 0.58 | 0.85 (0.73, 0.90) | Blood culture and clinical sepsis | 1389 | 576 | 10 | 8–11.3 |
| 2.5 | 0.76 (0.58 to 0.88) | 0.86 (0.32 to 0.99) | 0.62 | 0.83 (0.70, 0.93) | Blood culture | 263 | 124 | 3 | 0.4–0.5 |
| 5 | 0.79 (0.62 to 0.89) | 0.76 (0.58 to 0.88) | 0.55 | 0.84 (0.72, 0.89) | Blood culture | 1003 | 355 | 8 | 4.1–7 |
| 6 | 0.77 (0.69 to 0.83) | 0.76 (0.68 to 0.83) | 0.53 | 0.83 (0.75, 0.85) | Blood culture | 2600 | 942 | 21 | 3.4–5.2 |
| 8 | 0.54 (0.40 to 0.68) | 0.86 (0.77 to 0.92) | 0.40 | 0.78 (0.65, 0.84) | Blood culture | 1866 | 356 | 10 | 3.6–4 |
| 10 | 0.69 (0.61 to 0.75) | 0.81 (0.74 to 0.86) | 0.50 | 0.81 (0.73, 0.82) | Blood culture | 7920 | 1733 | 35 | 8.3–11.2 |
| 20 | 0.79 (0.67 to 0.88) | 0.73 (0.58 to 0.84) | 0.52 | 0.83 (0.73, 0.86) | Blood culture | 3603 | 251 | 8 | 1.5–1.7 |
| 50 | 0.73 (0.40 to 0.91) | 0.83 (0.63 to 0.94) | 0.56 | 0.86 (0.60, 0.94) | Blood culture | 963 | 596 | 6 | 10.7–19.5 |
| 100 | 0.69 (0.35 to 0.91) | 0.87 (0.35 to 0.99) | 0.56 | 0.83 (0.47, 0.96) | Blood culture | 539 | 220 | 3 | 6.9–8.1 |
| 10 | 0.62 (0.50 to 0.73) | 0.87 (0.76 to 0.94) | 0.49 | 0.77 (0.57, 0.91) | Clinical sepsis | 323 | 96 | 4 | 3.4–3.6 |
| High-income countries only | | | | | | | | | |
| 10 | 0.67 (0.57 to 0.75) | 0.81 (0.73 to 0.87) | 0.48 | 0.80 (0.71, 0.83) | Blood culture and clinical sepsis | 5997 | 994 | 26 | 9.5–12.5 |
| 8 | 0.58 (0.39 to 0.75) | 0.87 (0.73 to 0.94) | 0.45 | 0.80 (0.70, 0.86) | Blood culture | 1414 | 239 | 7 | 1.8–1.9 |
| 10 | 0.67 (0.57 to 0.76) | 0.81 (0.73 to 0.87) | 0.48 | 0.80 (0.71, 0.83) | Blood culture | 5924 | 964 | 25 | 9.8–12.8 |
| 20 | 0.79 (0.65 to 0.89) | 0.73 (0.56 to 0.85) | 0.52 | 0.83 (0.71, 0.87) | Blood culture | 3556 | 226 | 7 | 1.9–2.3 |
| 30 | 0.47 (0.35 to 0.59) | 0.84 (0.80 to 0.88) | 0.31 | 0.59 (0.46, 0.87) | Blood culture | 366 | 66 | 3 | 0 |
| Low- and middle-income countries only | | | | | | | | | |
| 6 | 0.76 (0.71 to 0.81) | 0.76 (0.67 to 0.83) | 0.52 | 0.82 (0.74, 0.84) | Blood culture and clinical sepsis | 2775 | 1046 | 21 | 2.8–4.1 |
| 10 | 0.70 (0.62 to 0.76) | 0.82 (0.72 to 0.89) | 0.52 | 0.79 (0.66, 0.84) | Blood culture and clinical sepsis | 2274 | 835 | 12 | 5–6.7 |
| 60 | 0.78 (0.67 to 0.86) | 0.8 (0.66 to 0.89) | 0.58 | 0.85 (0.73, 0.90) | Blood culture and clinical sepsis | 1389 | 576 | 10 | 8–11.3 |
| 5 | 0.80 (0.62 to 0.91) | 0.76 (0.56 to 0.89) | 0.56 | 0.85 (0.72, 0.90) | Blood culture | 863 | 303 | 7 | 4.6–8 |
| 6 | 0.77 (0.70 to 0.83) | 0.74 (0.65 to 0.82) | 0.51 | 0.82 (0.74, 0.85) | Blood culture | 2465 | 866 | 18 | 3.4–5.1 |
| 8 | 0.44 (0.34 to 0.55) | 0.82 (0.76 to 0.87) | 0.26 | 0.72 (0.43, 0.84) | Blood culture | 452 | 117 | 3 | 10.8–11.7 |
| 10 | 0.71 (0.61 to 0.79) | 0.79 (0.67 to 0.88) | 0.50 | 0.80 (0.68, 0.85) | Blood culture | 2024 | 769 | 10 | 5.2–7.4 |
| 12 | 0.67 (0.49 to 0.81) | 0.88 (0.58 to 0.98) | 0.55 | 0.78 (0.60, 0.93) | Blood culture | 303 | 89 | 4 | 5.8–6.3 |
| 50 | 0.79 (0.38 to 0.96) | 0.72 (0.50 to 0.87) | 0.51 | 0.80 (0.48, 0.94) | Blood culture | 752 | 558 | 4 | 10.7–25 |
| 60 | 0.80 (0.71 to 0.87) | 0.82 (0.70 to 0.90) | 0.62 | 0.87 (0.76, 0.91) | Blood culture | 1339 | 555 | 9 | 5.9–8.4 |
| 10 | 0.66 (0.52 to 0.77) | 0.89 (0.71 to 0.96) | 0.55 | 0.74 (0.59, 0.93) | Clinical sepsis | 250 | 66 | 3 | 0.8–0.9 |

*Defined as positive for disease using reference standard.

**Table 2** Test characteristics of procalcitonin (PCT) in the diagnosis of neonatal sepsis

| PCT cut point (ng/mL), ≥ | Sensitivity (95% CI) | Specificity (95% CI) | Youden's index | Area under the curve | Reference standard(s) | Total Patients, n | Disease, n* | Studies, n | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| All included studies | | | | | | | | | |
| 0.5 | 0.81 (0.75 to 0.86) | 0.66 (0.53 to 0.77) | 0.47 | 0.82 (0.74, 0.85) | Blood culture and clinical sepsis | 3963 | 444 | 15 | 3.5–5.5 |
| 1.0 | 0.67 (0.46 to 0.83) | 0.85 (0.63 to 0.95) | 0.52 | 0.79 (0.55, 0.90) | Blood culture and clinical sepsis | 567 | 66 | 5 | 3.4–4.2 |
| 1.7 | 0.81 (0.72 to 0.87) | 0.71 (0.50 to 0.85) | 0.52 | 0.83 (0.71, 0.88) | Blood culture and clinical sepsis | 433 | 152 | 3 | 0 |
| 2.0 | 0.75 (0.69 to 0.81) | 0.75 (0.59 to 0.86) | 0.50 | 0.78 (0.69, 0.81) | Blood culture and clinical sepsis | 3133 | 312 | 13 | 5.8–6.7 |
| 0.5 | 0.83 (0.76 to 0.88) | 0.65 (0.52 to 0.77) | 0.48 | 0.83 (0.73, 0.86) | Blood culture | 3777 | 399 | 14 | 4.2–6.4 |
| 2.0 | 0.75 (0.68 to 0.80) | 0.73 (0.56 to 0.85) | 0.48 | 0.77 (0.68, 0.82) | Blood culture | 2974 | 258 | 11 | 7.3–8.7 |
| High-income countries only | | | | | | | | | |
| 0.5 | 0.75 (0.69 to 0.80) | 0.71 (0.58 to 0.82) | 0.46 | 0.75 (0.70, 0.82) | Blood culture and clinical sepsis | 3346 | 244 | 8 | 0.3–0.4 |
| 0.5 | 0.75 (0.68 to 0.80) | 0.71 (0.55 to 0.83) | 0.46 | 0.75 (0.69, 0.82) | Blood culture | 3160 | 199 | 7 | 0.7–0.9 |
| 1.0 | 0.71 (0.46 to 0.87) | 0.84 (0.54 to 0.96) | 0.55 | 0.81 (0.56, 0.92) | Blood culture | 500 | 62 | 4 | 5.6–6.6 |
| 2.0 | 0.74 (0.59 to 0.85) | 0.67 (0.36 to 0.88) | 0.41 | 0.77 (0.63, 0.83) | Blood culture | 2405 | 85 | 5 | 0.5–0.7 |
| Low- and middle-income countries only | | | | | | | | | |
| 2.0 | 0.77 (0.71 to 0.83) | 0.78 (0.60 to 0.90) | 0.55 | 0.79 (0.71, 0.86) | Blood culture and clinical sepsis | 728 | 227 | 8 | 8.7–9.2 |
| 0.5 | 0.89 (0.80 to 0.95) | 0.58 (0.36 to 0.78) | 0.47 | 0.87 (0.70, 0.92) | Blood culture | 617 | 200 | 7 | 10.7–15.6 |
| 2.0 | 0.77 (0.68 to 0.84) | 0.75 (0.56 to 0.88) | 0.52 | 0.80 (0.69, 0.88) | Blood culture | 569 | 173 | 6 | 12.5–13.7 |

*Defined as positive for disease using reference standard.

to diagnose neonatal sepsis in LMICs. Moreover, despite bearing most of the world's childhood disease burden for neonatal sepsis, there was a relative paucity of data from LMICs.

Despite its high incidence and significant disease burden globally, there is no unified criteria for the diagnosis of neonatal sepsis. The WHO Guidelines for the Management of Common Childhood Illnesses include risk factors and antibiotic recommendations for neonatal sepsis, though diagnostic criteria are lacking.[24] For purposes of standardisation, we evaluated the diagnostic performance of biomarkers using positive blood cultures as a reference standard. However, important challenges in the diagnosis of neonatal sepsis include potential false-negative culture results due to maternal antibiotic administration, insufficient blood volume obtained in blood draws, and low, or intermittent, levels of bacteraemia.[25 26] There were 16 studies that used clinical sepsis as a reference standard, although clear and consistent definitions of this reference were lacking.

Prior systematic reviews have described the diagnostic utility of biomarkers in neonatal sepsis[27–29]; however, most reviews omit studies conducted in LMICs, where the disease burden for neonatal sepsis is highest.[30] Our study found CRP for neonatal sepsis in LMICs demonstrated poor specificity at varying cut points, but good overall discriminatory value. WBC had little diagnostic value in the diagnosis of neonatal sepsis in our study. PCT had relatively low specificity but good discriminatory value in studies conducted in LMICs. Prior reviews highlight statistical heterogeneity between studies on PCT and neonatal sepsis.[31]

In practice in many resource-limited settings, elevations in biomarkers such as CRP and ESR are used to make decisions around the initiation of antibiotics for neonates. However, our study suggests that the sole reliance on a single biomarker to make such a decision may not have sufficient discriminatory value. The development and validation of clinical prediction models including historical findings, other risk factors, as well as biomarkers for neonatal sepsis in LMICs may enhance the diagnostic capabilities in such settings.[9]

### Limitations

Most of the included studies did not assess all four biomarkers of interest, making unclear their comparative test characteristics in the same populations. It is possible that some studies included neonates that had been pretreated with antibiotics, which could affect the level of biomarkers.[32] Most included studies did not differentiate early from late-onset neonatal sepsis. Biomarkers in early-onset sepsis may reflect maternal values. Additionally, populations of neonates who had malnutrition or were infected with, or exposed to, HIV were often excluded from the included studies, leaving unclear the diagnostic performance of biomarkers for the evaluation of infectious diseases in these vulnerable populations. Many studies reported the test characteristics of biomarkers for several infectious diseases in aggregate, which precluded our analysis from teasing out the test characteristics for individual infectious diseases. Lastly, though we attempted to review articles in as many languages as our team was capable to, several articles were excluded from our analysis because they were not published in English, Spanish, French, German, Dutch, or Arabic. This may have introduced some selection bias, potentially excluding more articles reporting research conducted in LMICs where these languages are not spoken.

## CONCLUSIONS

CRP and PCT had good discriminatory value to diagnose neonatal sepsis in LMICs. However, none of the evaluated biomarkers had sufficient specificity or discriminatory value to be used in isolation to diagnose neonatal sepsis in LMICs. Future studies conducted in LMICs and should incorporate biomarkers into clinical prediction algorithms to achieve more optimal diagnostic and discriminatory ability for neonatal sepsis.

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**Contributors** CAR, JL, ALW, REH, AS, JR-S, KS, CR, SG, KD and MN conceptualised and designed the study. CAR, JL, ALW, REH, AS, JR-S, KS, CR, SG, KD and MN oversaw data collection and verified the underlying data. CAR and JL verified the underlying data. ALW conducted the statistical analyses. CAR wrote the first draft of the manuscript. CAR, JL, ALW, REH, AS, JR-S, KS, CR, SG, KD and MN interpreted the data, reviewed and provided input to the final draft. CAR had final responsibility for the decision to submit for publication and is the author responsible for the overall content as the guarantor.

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**Data availability statement** Data are available on reasonable request. The data used for this study may be made available upon reasonable request to the corresponding author.

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**Supplemental Materials for Article**: A Systematic Review and Meta-Analysis of the Diagnostic Ability of CRP, ESR, WBC, and PCT in Detecting Neonatal Sepsis and Pneumonia

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**Supplemental Table 1**. Description of articles assessing the test characteristics of biomarkers for the diagnosis of neonatal sepsis.

| Citation | Study Location | Study Design | Study Country | Patient Age Range | Study Population | Biomarker(s) | Gold Standard | Inclusion Criteria | Exclusion Criteria | QUADAS-2 Score |
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| Abdalla EOEA, et al. *Cogent Medicine.* 2017.[1] | NICU | Prospective cohort | Sudan | 0-72 hours | 49 | CRP, PCT | Blood culture | -Full term infants with risk factors for early-onset neonatal infection including GBS infection during pregnancy, membrane rupture before onset of uterine contractions, prolonged premature rupture of membranes >18 hours, offensive odor of amniotic fluid<br>-Infants who developed clinical features of infection within 72 hours of birth including hypothermia/hyperthermia, irritability, lethargy, apnea, and bradycardia | -Infants started on antibiotics before admission<br>-Infants with major congenital anomalies, proven inborn errors of metabolism or hypoxic ischemic encephalopathy<br>-Infants whose parents refused consent | Level 2 |
| Abdollahi A, et al. *Mediterr J Hematol Infect Dis.* 2012.[2] | NICU | Cross Sectional | Iran, Islamic Rep. | 0-12 hours | 95 | CRP, PCT | Blood culture (for "proven early-onset sepsis") or clinical signs of sepsis* and positive sepsis screen or maternal risk factor (for "clinical early-onset sepsis) | -12 hours old or younger<br>-Clinical signs of sepsis<br>-Maternal risk factor for sepsis | -Congenital malformations<br>-TORCH infection | Level 3 |
| Aboud MI, et al. *Iran J Med Sci.* 2010.[3] | NICU | Prospective Cohort | Syrian Arab Republic | 1-30 days | 47 | CRP, PCT, WBC | Blood culture | -Admission to NICU with bacteremia evaluation | -Congenital malformations<br>-Exchange transfusion for neonatal hyperbilirubinemia<br>-Death during follow up | Level 2 |
| Adib M, et al. *Iran J Basic Med Sci.* 2012.[4] | NICU | Cross Sectional | Iran, Islamic Rep. | 1 hour-30 days | 87 | CRP, PCT | Blood culture | -Maternal risk factor such as fever, prolonged rupture of amniotic membrane >24 hours<br>-Low birth weight (<2500 grams)<br>-Signs and symptoms of sepsis: feeding intolerance, lethargy, temperature instability, apnea, respiratory distress, poor perfusion, seizures, tachypnea, bradycardia, abdominal distension or vomits<br>-Premature birth (<37 weeks) | Not specified | Level 2 |
| Ahmed E, et al. *Pak J Med Sci.* 2017.[5] | NICU | Prospective Cohort | Pakistan | 1-12 days | 135 | CRP | Blood culture | -Suspected sepsis (presence of unexplained fever or hypothermia, irritability, poor or no feeding, lethargy, respiratory dysfunction | -Birth weight <1.5 kg<br>-Birth asphyxia<br>-Already taking any antibiotic treatment | Level 1 |

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| | | | | | | | | (e.g. apnea or tachypnea), cardiovascular dysfunction (e.g. intermittent tachycardia or bradycardia and cold peripheries), presence of maternal risk factors (foul smelling vaginal discharge, rupture of membranes for >18 hours, history of fever in prenatal or post-natal period) | | |
| Ahmed Z, et al. *J Coll Physicians Surg Pak.* 2005.[6] | NICU | Cross Sectional | Pakistan | 1-30 days | 200 | CRP, ESR, WBC | Blood culture | -Non-specific sign and symptom of sepsis or focal signs of infection | -Congenital malformations<br>-Birth asphyxia<br>-Inborn errors of metabolism<br>-Jaundice<br>-GA <33 weeks<br>-Respiratory distress due to surfactant deficiency | Level 1 |
| Akhmaltdinova L, et al. *Int J Inflam*. 2021.[7] | NICU | Cross sectional | Kazhakstan | 0-4 days | 57 | CRP | Blood culture | -criterion for determining a case of sepsis was a positive blood culture<br>-control group consisted of children who received treatment in the intensive care unit with negative blood cultures and unconfirmed infectious complications | -born to HIV-positive mothers<br>-receiving therapy with high doses of glucocorticosteroids<br>-primary immunodeficiency state<br>-blood loss<br>-severe malformations<br>-acute hemolytic disease of the newborn | Level 2 |
| Al-Zahrani AK, et al. *J Infect in Dev Ctries.* 2015.[8] | NICU | Retrospective cohort | Saudi Arabia | 1-30 days | 100 | CRP, PCT | Blood culture | -Neonates clinically suspected to have sepsis which included respiratory manifestations such as apnea or tachypnea (respiratory rate over 70 breaths per minute in preterm and over 60 breaths per minute in term neonates), nasal flaring, retractions, cyanosis or respiratory distress, bradycardia (heart rate less than 100 beats per minute in preterm and less than 80 bpm in term neonates), or tachycardia (the upper threshold of heart rate based on age: 1-2 days, > 159 bpm; 3-6 days, > 166 bpm), hypotonia or seizures, poor skin color, and irritability or lethargy | -Neonates suspected to have congenital malformations and/or laboratory confirmed TORCH infections | Level 3 |
| Ali AM, et al. *Egypt J of Immunol.* 2008.[9] | NICU | Prospective Cohort | Egypt, Arab Rep. | 1-7 days | 69 | CRP, PCT | Blood culture | -Controls (healthy infants)<br>-Signs of sepsis (i.e. tachypnea, grunting, apnea, cyanosis, pallor, hypotension, tachycardia, bradycardia, rejection of food, abdominal distension, hepatomegaly, lethargy, | -Infants born to mothers with gestational diabetes | Level 3 |

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| | | | | | | | | convulsions, anemia) | | |
| Alkan Ozdemir S, et al. *J Clin Lab Anal.* 2018.[10] | NICU | Prospective cohort | Turkey | 3-35 days | 127 | CRP | Blood culture | -All neonates consecutively admitted | -Neonates with congenital anomalies, congenital infections, born to mothers with clinical chorioamnionitis, or those who had early-onset neonatal sepsis, perinatal asphyxia, or intrauterine growth restriction | Level 1 |
| Aminullah A, et al. *Med J Indones.* 2001.[11] | NICU | Prospective Cohort | United States | 1-7 days | 220 | CRP, ESR, WBC | Blood culture | -Suspected sepsis (history of prematurity, prolonged rupture of membranes, maternal fever, chorioamnionitis, or maternal colonization with group B strep) | -Incomplete data | Level 1 |
| Amponsah SK, et al. *Pan Afr Med J.* 2017.[12] | NICU | Cross Sectional | Ghana | 1-12 hours | 62 | CRP, PCT | Blood culture | -Maternal risk factors (prolonged rupture of amniotic membrane >18 hrs, chorioamnionitis)<br>-Neonatal risk factors (low birth weight and premature birth)<br>-Clinical symptoms (feeding intolerance, lethargy, temperature instability, tachypnea, bradycardia, tachycardia, abdominal distension or vomiting)<br>-Presumptive diagnosis of sepsis by admitting physician | -Meconium aspiration<br>-Perinatal asphyxia<br>-Neonates who required resuscitation for any reason | Level 2 |
| Anwer SK, et al. *J Pak Med Assoc.* 2000.[13] | NICU | Retrospective cohort | Pakistan | 12 hours-20 days | 50 | CRP, WBC | Blood culture | -Inborn infants with prematurity (< 36 weeks), low birth weight, birth asphyxia, home delivery, instrumentation.<br>-Infants with feeding problem, lethargy, temperature instability, respiratory distress, irritability (including convulsions), abdominal distention, and apnea or cyanotic spells | Surgical cases | Level 2 |
| Arnon S, et al. *Biol Neonate.* 2005.[14] | NICU | Prospective cohort study | Israel | 5-36 days | 116 | CRP | Blood culture | -Clinical sepsis diagnosed by one or more signs of infection and two laboratory signs suggestive of sepsis (increasing incidence of apnea and/or bradycardia of more than 30% from the previous day, hypotension, respiratory dysfunction, muscular hypotonia, lethargy and fever or hypothermia<br>-Biochemical variables suggestive of sepsis (acidosis (pH < 7.25); hyperglycemia (glucose > 160 mg%); thrombocytopenia ( < 150 x 10^9 /l); neutropenia ( < 1.5 x 10^9 /l) and a ratio of immature to total neutrophils (I/T ratio) | Not specified | Level 2 |

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| | | | | | | | | exceeding 0.2) | | |
| Ayazi P, et al. *Le Infezioni in Medicina.* 2014.[15] | Not Specified | Prospective cohort | Iran, Islamic Rep. | "Infant", age not specified | 83 | CRP | Culture (blood, cerebrospinal fluid, urine) or clinical signs of sepsis with two or more of the following: WBC <4000 or >10000 per mm^3, band cells to total neutrophil ration > 0.2 and a positive acute phase reactant test | -More than three of the following symptoms: maternal risk factors such as maternal fever, alcohol consumption, premature rupture of membranes (more than 24 hours), chorioamnionitis, and maternal urinary tract infection; neonatal risk factors such as low birth weight (less than 2500 g) and premature birth (less than 37 weeks); anorexia, lethargy, temperature instability (fever and hypothermia), jaundice, apnea, respiratory distress, tachycardia (>180/ min), tachypnea (>60/min), cyanosis, and vomiting | Not specified | Level 3 |
| Ballot DE, et al. *S Afr Med J.* 2004.[16] | NICU | Prospective Cohort | South Africa | "Infant", age not specified | 183 | PCT | Blood culture | -All neonates undergoing sepsis evaluation; evaluation for sepsis was done at the discretion of the attending physician for a variety of reasons including maternal risk factors for sepsis (e.g. prolonged rupture of membranes, chorioamnionitis, maternal pyrexia, maternal urinary tract infection, foul-smelling liquor) and signs of neonatal sepsis (e.g. temperature instability, lethargy, feeding intolerance, seizures, ongoing respiratory distress, irritability, blood glucose abnormalities, hypotension, poor perfusion, acidosis) | -Incomplete data (missing blood culture results, no PCT obtained)<br>-Contaminated blood cultures | Level 1 |
| Beltempo M, et al. *BMC Pediatr.* 2018.[17] | NICU | Retrospective Cohort | Canada | 3-28 days | 416 | CRP, WBC | Blood culture | -Increased apnea episodes<br>-Temperature instability<br>-Feeding intolerance<br>-Lethargy<br>-Hypotonia | -Known contaminants such as Corynebacterium and unidentified organisms | Level 1 |
| Benitz WE, et al. *Pediatrics*. 1998.[18] | NICU | Prospective cohort | United States of America | 1-118 days | 987 | CRP | Blood culture | -Neonates who were treated for sepsis due to intrapartum fever, chorioamnionitis, prolonged rupture of membranes, premature preterm rupture of membranes, premature onset of labor, preterm labor refractory to tocolysis, fetal tachycardia, meconium staining of amniotic fluid) and neonatal clinical signs[x] | -Infants > 44 weeks post-conceptional age | Level 1 |

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| Berger C, et al. *Eur J Pediatr.* 1995.[19] | NICU | Prospective Cohort | Switzerland | 0-6 weeks | 195 | CRP, WBC | Blood culture | -Any neonate with suspected sepsis | -Possible viral infection<br>-Post-operative | Level 1 |
| Blommendahl J, et al. *Scand J Infect Dis.* 2002.[20] | Inpatient | Prospective Cohort | Finland | Not stated, "neonates" | 169 | CRP, PCT | Blood culture | -Children whom the attending physician suspected of having an infection based on clinical symptoms such as tachypnoea, respiratory distress, apnoea, irritability, grunting, lethargy, tachycardia, bradycardia, retractions, convulsions, temperature instability, gastrointestinal disturbances and hypotony<br>-All very premature babies (birth before 32 completed weeks of gestation) | -All neonates who had received antibiotic treatment, including maternal antibiotic treatment | Level 3 |
| Bohnhorst B, et al. *Acta Paediatr.* 2012.[21] | NICU | Prospective Cohort | Germany | Preterm and newborn infants after DOL 4 | 170 | CRP, PCT | Blood culture, urine culture, CSF culture, CXR for pneumonia, NEC confirmed with pathogen cultured from abdominal puncture fluid or intraoperative swabs | -All preterm and newborn infants treated in NICU from January 2006 to June 2009 who were clinically suspected to have an infection from the 4th day of life | -Discharge/transfer <4$^{th}$ day of life<br>-Death <4$^{th}$ day of life<br>-Patients with sepsis transferred<br>-Incomplete/neglected blood-taking | Level 3 |
| Boo NY, et al. *Singapore Med J*. 2008.[22] | NICU | Prospective Cohort | Malaysia | "Infant", age not specified | 43 | CRP, PCT | Blood culture | -Infants admitted to NICU with signs suggestive of sepsis<br>-Infants who developed signs of sepsis while in the ward | -Infants on antibiotics<br>-Infants who developed signs of sepsis within 72 hours of discontinuation of antibiotics | Level 4 |
| Boskabadi H, et al. *Iran J Pediatr*. 2010.[23] | NICU | Prospective Cohort | Iran, Islamic Rep. | Neonates > 72 hours of life | 93 | CRP | Blood culture or clinical sepsis | -Positive clinical signs of sepsis<br>-Positive blood or cerebrospinal fluid culture | -Congenital malformations<br>-Congenital infections associated with the TORCH complex<br>-Lack of parental consent | Level 4 |
| Broner CW, et al. *Clin Pediatr.* 1990.[24] | Emergency Department , Clinics | Prospective cohort | United States of America | 0-56 days | 52 | CRP, ESR, WBC | Blood culture | -Infants with rectal temperature ≥38.1 °C | -Not specified | Level 4 |
| Buck C, et al. *Pediatrics.* 1994.[25] | NICU | Prospective cohort | Germany | 0-3.5 days | 222 | CRP | Blood culture and clinical sepsis | -Newborns admitted to the regular and intermediate-care wards<br>-Newborns suspected of having infection during their hospital stay were included<br>-Newborns with the presumptive diagnosis of sepsis/neonatal | -Incorrect or incomplete blood sampling | Level 4 |

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| Bunduki GK, et al. *BMC Res Notes*. 2020.[26] | Inpatient | Cross sectional | Democratic Republic of Congo | 0-30 days | 228 | CRP | Blood culture | -Neonates admitted a three hospitals in Butembo/Eastern DRC between September to November 2018 with suspected sepsis according to International Paediatric Sepsis Consensus (IPSC) criteria | -Neonates diagnosed with sepsis but who died immediately or upon arrival at the health facility and blood samples were not yet taken were excluded<br>-Neonates with a congenital malformation or dysmorphic features, those diagnosed with malaria parasitemia, those from HIV-positive mother, those under antibiotic therapy, and those above 30 days of life were also excluded | Level 1 |
| Chacha F, et al. *BMC Pediatrics.* 2014.[27] | NICU | Prospective Cohort | Tanzania | Not specified | 305 | CRP, WBC | Blood culture | -All neonates with clinical suspicion of neonatal sepsis according to WHO criteria admitted to NICU | -History of use of antibiotics before enrolment for more than 72 hours<br>-Body weight less than 1 kilogram | Level 1 |
| Chen CJ, et al. *J Chin Med Assoc.* 2009.[28] | Inpatient | Prospective cohort | China | 0-3 months | 135 | CRP, WBC | Blood culture, chest radiograph, urine culture, CSF culture | -Infants admitted with fever >38C | -Infants born before 36 weeks of gestation<br>-Infants with congenital heart disease, bronchopulmonary dysplasia, chronic lung disease, immunodeficiency, chromosome anomalies, or congenital gastrointestinal tract anomalies<br>-Infants with hyperbilirubinemia and those who exhibited an antenatal setup for sepsis (i.e. premature rupture of membranes, maternal fever, or peripartum antibiotics) | Level 3 |
| Chiesa C, et al. *Clin Chem.* 2003.[29] | NICU | Prospective Cohort | Italy | 0- 49 hours | 134 | CRP, PCT | Blood culture | -Consecutively enrolled critically ill newborns over a 6-month period in 2 maternity hospitals | -Preadmission deaths<br>-Lethal abnormalities<br>-Babies whose cord blood was not sampled for all three study markers | Level 2 |
| Choo YK, et al. *Korean J Pediatr.* 2012.[30] | NICU | Prospective Cohort | Korea, Rep. | 0-30 days | 23 | CRP, WBC | Blood culture | -Neonates born at >/=30 weeks gestation and admitted to NICU from May to August 2010 with clinical signs of sepsis | Not specified | Level 2 |
| Coggins SA, et al. *PLoS One.* 2013.[31] | NICU | Prospective cohort | United States of America | not stated | 363 | CRP | Blood culture | -All inborn preterm infants weighing at least 1500 grams with negative blood cultures<br>-All patients admitted with positive blood cultures | -Neonates with congenital anomalies or surgery performed within the first 3 postnatal days<br>-Non-viable infants or infants who did not survive past the first 48 hours post-partum<br>-patients no longer hospitalized 48 hours after birth<br>-patients who did not have at least one time-correlated set of CRP and neutrophil data | Level 1 |
| Değirmencioğ lu H, et al. | NICU | Prospective Cohort | Turkey | 4-60 days | 55 | CRP | Blood culture | -Born ≤32 weeks gestational age<br>-4 to 60 days postnatal age | -Major congenital and/or chromosomal anomalies. | Level 2 |

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| *BMC Infect Dis.* 2019.[32] | | | | | | | | -Gram-positive and/or negative bacteria detected in blood culture | | |
| Deshpande SS, et al. *J Clin Diag Res*. 2021.[33] | NICU | Prospective Cohort | India | 0-28 days | 104 | CRP | Blood culture | -neonates admitted with clinical suspicion of sepsis | -neonates with hyaline membrane disease, transient tachypnea of newborn or hypoxia induced encephalopathy | Level 3 |
| Distefano G, et al. *Acta Paediatr.* 2004.[34] | NICU | Prospective Cohort | Italy | 0-10 days | 35 | CRP, PCT | Blood culture | -Premature infants (gestational age <37 weeks) with clinical findings (respiratory distress, apnoea, circulatory instability, poor capillary refill, hypothermia, tachycardia, tachypnoea, hypoxaemia, oliguria)<br>-Hematological findings (leucocyte count) of infection<br>-Positive blood cultures were included in the study group<br>-Matched preterm babies with no clinical or haematological signs of infection and negative blood cultures were enrolled as controls | -Neonates born of mothers receiving antibiotics before or during delivery<br>-Babies suffering birth trauma | Level 2 |
| Doellner H, et al. *J Pediatr*. 1998.[35] | NICU | Prospective Cohort | Norway | 0-7 days | 122 | CRP, WBC | Blood culture and clinical sepsis | - The study included 241 neonates consecutively admitted to the neonatal intensive care unit at the University Hospital of Trondheim during an 11-month period in 1993. | NA | Level 1 |
| Du WX, et al. *Clin Chim Acta.* 2016.[36] | Inpatient (all patients were neonates) | Prospective Cohort | China | 0-72 hours | 157 | CRP, PCT, WBC | Blood culture | -Preterm and term neonates with suspicion of an early-onset (within 72 h after birth) infection | -Major congenital malformations<br>-Confirmed intrauterine viral infection<br>-Lack of parental consent | Level 3 |
| Duhan A, et al. *J Krishna Inst Med Sci Univ.* 2016.[37] | NICU | Prospective cohort | India | Not specified | 128 | CRP, WBC | Blood culture | -Clinical suspicion of sepsis based on clinical features including feeding problems, lethargy, respiratory distress, irritability, convulsions, abdominal distention, recurrent attacks of apnea, or cyanotic spells, vomiting, poor cry, and tachypnoea<br>-major perinatal risk factors were prematurity, low birth weight, birth asphyxia, home delivery, caesarean section, and meconium aspiration<br>-63 normal neonates from immunization clinic were studied | -Contaminated cultures, prior antibiotic exposure, major congenital abnormalities, inborn errors of metabolism, and hemolytic jaundice | Level 2 |

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| Edgar JDM, et al. *Clin Sci (London).* 1994.[38] | NICU | Prospective Cohort | United Kingdom | Not specified | 60 | CRP | Blood culture | -Suspected of having infection | Not specified | Level 2 |
| El Sehmawy AA, et al. *Infect Drug Resist*. 2021.[39] | NICU | Case control | Egypt, Arab Rep. | 1-3 days | 60 | CRP, PCT | Blood culture | - | - | Level 5 |
| Forest JC, et al. *Clin Biochem.* 1986.[40] | NICU | Retrospective cohort | Canada | Not specified | 127 | CRP | Blood culture | -Neonates admitted with 26-40 weeks gestation and birth weight from 703-4000 grams | -Not specified | Level 2 |
| Franz AR, et al. *Pediatr Infect Dis J.* 1999.[41] | NICU | Prospective Cohort | Germany | 0-11 days | 162 | CRP, PCT | Blood culture, clinical sepsis | Infants suspected of having bacterial infection (BI) or admitted on DOL1 with maternal history of amniotic infection- | -Umbilical artery pH <7.00<br>-Trisomy 21<br>-Incomplete data collection. | Level 2 |
| Franz AR, et al. *Acta Paediatr.* 2001.[42] | NICU | Prospective cohort | Germany | 0-72 hours | 70 | CRP | Blood culture | -Neonates clinically suspected to have sepsis based on one clinical sign suggesting bacterial infection including pallor, greyish skin color, poor perfusion (capillary refill >2 seconds) and arterial hypotension, tachypnea (>60 breaths/minute), dyspnea (grunting, nasal flaring, retractions), apnea, inspiratory oxygen fraction (FiO2) > 0.21, and respiratory insufficiency, and muscular hypotonia or hypertonia, hyperexcitability, irritability, and lethargy<br>-maternal history of amniotic infection rupture of membranes before the onset of labor, rupture of membranes >18 hours before delivery, foul-smelling amniotic fluid, ineffective tocolysis before 35 weeks of gestation, fetal tachycardia (baseline >160 beats/minute) and maternal rectal temperature >38.5C | -Chromosomal anomalies, meconium aspiration, or umbilical artery pH < 7.0, transferred to other hospitals | Level 2 |
| Frerot A, et al. *Eur J Clin Microbiol and Infect Dis.* 2019.[43] | NICU | Prospective cohort | France | Birth | 186 | Cord blood PCT | Definite sepsis: positive blood or cerebrospinal fluid culture. Probable sepsis: WBC < 5000/$mm^3$ or s ≥ 21,000/mm3, | -All preterm neonates born between 24 weeks and 27 weeks and 6 days with cord blood PCT lab testing | -Excluded patients with insufficient umbilical cord blood sample volume | Level 2 |

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| | | | | | | | CRP > 10 mg/dL, and clinical signs of sepsis, antibiotic treatment > 72 hours | | | |
| Gajdos V, et al. *Arch Pediatr*. 2005.[44] | Emergency Department | Prospective cohort | France | 6-92 days | 315 | CRP | Blood, urine and CSF culture | -Not specified | -Not specified | Level 2 |
| Gao C, et al. *BMC Infect Dis*. 2021.[45] | NICU | Cross sectional | China | 0-28 days | 142 | CRP | Blood culture | -age <28 days and routine blood examinations, | -infants who had incomplete information or discontinued therapy | Level 3 |
| Gupta SK, et al. *Indian Pediatr*. 1989.[46] | Inpatient | Prospective cohort | India | 0 hours – not specified | 150 | CRP | Clinical sepsis (not defined) | -Neonates born at the hospital or admitted with clinical evidence of septicemia | -Not specified | Level 4 |
| Habib A, et al. *J Coll Physicians Surg Pak*. 2021.[47] | NICU | Cross-sectional | Pakistan | 1-29 days | 171 | PCT | Blood culture | -criteria of suspected neonatal sepsis included any two: temperature >38.5°C or <36°C, increased heart rate above two standard deviations of normal for age, respiratory rate greater than two standard deviations of normal for age, TLC increased or decreased for age or >10% immature neutrophils in peripheral blood | -on antibiotics before blood culture<br>-congenital disorder<br>-evidence of respiratory distress syndrome on chest x-ray<br>-inborn errors of metabolism | Level 2 |
| Hagag AA, et al. *Infect Disord Drug Targets*. 2021.[48] | NICU | Case control | Egypt, Arab Rep. | 0-28 days | 80 | CRP | Clinical sepsis | -full-term neonates with high probable sepsis | -Preterm or low birth weight neonates<br>-multiple congenital anomalies, chromosomal abnormalities, hypoxic-ischemic encephalopathy, infant of diabetic mother and neonates with abnormal thyroid function screening | Level 2 |
| Hagag A, et al. *Infect Disord Drug Targets*. 2020.[49] | NICU | Prospective cohort | Egypt, Arab Rep. | Not specified | 80 | CRP | Blood culture or clinical sepsis | -Any full-term neonate presented with high probable sepsis | -Preterm or low birth weight neonates and those with multiple congenital anomalies, chromosomal abnormalities, hypoxic-ischemic encephalopathy, infant of diabetic mother and neonates with abnormal thyroid function screening | Level 4 |
| Hashem HE, et al. *Int J Microbiol*. 2020.[50] | NICU | Prospective cohort | Egypt, Arab Rep. | Not specified | 235 | CRP | Blood culture | -For sepsis patient's identification and selection, neonates had presumed one or more infection risk factors, in addition to at least 2 clinical and 2 laboratory criteria: (1) respiratory compromise: respiratory rate >60 breaths per minute, or cessation of | -Patients who had confirmed intrauterine viral infection (toxoplasmosis, rubella, cytomegalovirus, syphilis, and herpes), patients with long-standing hospitalization (admitted for more than one-month duration), and those neonates who had recently undergone | Level 4 |

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| | | | | | | | | respiration for ≥20 seconds, occurring at a rate of ≥2 times per hour, or pulse oxymeter readings of ≤85%; (2) cardiovascular compromise: heart rate <100 beats per minute, pallor, or hypotension; (3) metabolic changes: hypothermia (rectal temperature <36°C), a body temperature of >38°C, feeding intolerance (increased gastric residuals >50% of milk volume in ≥2 feedings within 24 hours), glucose instability (blood glucose level <45 mg/dL or >125 mg/dL), or metabolic acidosis (pH < 7.25); or (4) neurologic changes: lethargy or decreased activity, whereas laboratory criteria were white blood cell (WBC) count <5 or >20 × $10^9$/L, immature to total neutrophil (I : T) ratio >0.2, platelet count <100 × $10^9$/L, and CRP >10 mg/L | surgical intervention were excluded from the study. | |
| Hashem HE, *Dis Markers*. 2021.[51] | NICU | Case control | Egypt, Arab Rep. | 0-28 days | 184 | CRP | Blood culture | -neonates with presumed one or more infection risk factors in addition to at least 2 clinical and 2 laboratory criteria: "(1) respiratory rate > 60 breaths per minute or cessation of respiration for ≥20 seconds, occurring at a rate of ≥2 times per hour, or pulse oximeter readings of ≤85%; (2) heart rate of <100 beats per minute, pallor, or hypotension; (3) hypothermia (rectal temperature of <36°C), a body temperature of >38°C, feeding intolerance (increased gastric residuals of >50% of milk volume in ≥2 feedings within 24 hours), glucose instability (blood glucose level of <45mg/dL or >125 mg/dL), or metabolic acidosis (pH < 7:25); or (4) lethargy or decreased activity, whereas laboratory criteria were white blood cell (WBC) count <5 or >20 × 109 cells/L, immature to total neutrophil (I : T) ratio > 0:2, platelet count<100×109/L, and | -recently undergone surgical interventions (within the last 15 days)<br>-patients admitted for more than one month<br>-neonates who had confirmed intrauterine viral infection (toxoplasmosis, rubella, and Cytomegalovirus) | Level 2 |

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| Hassan HR, et al. *J Clin Neonatol.* 2016.[52] | NICU | Prospective cohort | India | 0-72 hours | 100 | CRP, ESR, WBC | Blood culture | -Neonates with sepsis risk factors including as prematurity, low birth weight, birth asphyxia, foul-smelling liquor, unclean per vaginal examination before delivery, prolonged rupture of membranes, and prolonged labor | -Neonates already receiving antibiotics | Level 2 |
| Hisamuddin E, et al. *Pak J Med Sci.* 2015.[53] | NICU | Prospective cohort | Pakistan | 0-28 days | 147 | CRP | Blood culture | -All neonates having suspected neonatal sepsis defined by clinic pathological features of perinatal risk factors including maternal pyrexia (within 1 week prenatal and/or 48 hours postnatal), prolonged rupture of membranes (18 hours), foul smelling vaginal discharge or/and maternal urinary tract infection diagnosed in last month<br>-Neonates having unexplained hypothermia/hyperthermia, lethargy, irritability, poor feeding or milk intolerance, respiratory dysfunction evidenced by apnea (>10 sec.), tachypnoea (>60 breaths/minute), cardiovascular dysfunction such as persistent tachycardia (>160 beat/min) or bradycardia (<100 beat/min). | -Neonates with birth asphyxia and very low birth weight | Level 3 |
| Ipek IO, et al. *J Matern Fetal Neonatal Med.* 2010.[54] | NICU | Prospective Cohort | Turkey | 2-26 days | 97 | CRP | Blood culture or clinical sepsis | -Term newborns hospitalized for 'rule out sepsis' to NICU with clinical signs and symptoms suggesting sepsis and two abnormalities in lab findings | -Use of antibiotics by the newborn or the mother (shortly before delivery)<br>-Maternal hypertension<br>-Meconium in amniotic fluid<br>-Asphyxia<br>-Congenital abnormality | Level 3 |
| Jacquot A, et al. *Arch Dis Child Fetal Neonatal Ed*. 2009.[55] | NICU | Prospective cohort | France | 0-72 hours | 73 | CRP, PCT | Clinical sepsis | -All newborn infants with clinical suspicion of LOS (after 72 h of life) who were hospitalized in a NICU (Croix-Rousse Hospital, Lyon, France) were enrolled. | - Newborn infants under antibiotic treatment, with severe congenital malformation or requiring neo- natal surgery, or diagnosed with necrotizing enterocolitis were excluded. | Level 4 |
| Jaswal RS, et al. *Indian Pediatr.* 2003.[56] | Not Specified | Prospective cohort | India | 0 day-1 month | 50 | CRP | Blood culture | -Birth weight > 1500g with suspected septicemia based on sepsis score defined as 3 or more of the following: refusal to feed, abdominal distention, vomiting, lethargy, jaundice, poor cry, seizures, diarrhea, apnea, | -Neonates that had undergone surgery<br>-Neonates with suspected meningitis | Level 3 |

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| | | | | | | | | tachypnea, poor capillary refill, hypothermia, fever and umbilical discharge. | | |
| Karabulut B, et al. *Fetal Pediatr Pathol*. 2020.[57] | NICU | Retrospective cohort | Turkey | 12-24 hours | 159 | CRP, ESR, PCT, WBC | Blood culture | -Neonates who were appropriate for gestational age and diagnosed with early-onset sepsis. | -Neonates < 37 weeks or > 42 weeks gestation, small for gestational age, intrauterine growth restriction, perinatal asphyxia, congenital abnormality, chromosomal abnormality, preeclampsia, lack of data | Level 1 |
| Kaur S, et al. *Int J Pediatr*. 2021.[58] | NICU | Prospective cohort | India | 0-7 days | 60 | CRP | Blood culture | -clinical symptoms and signs of suspected neonatal sepsis/high-risk factors for developing sepsis | -received antibiotics previously | Level 3 |
| Khair KB, et al. *Mymensingh Med J.* 2012.[59] | NICU | Prospective Cohort | Bangladesh | 0-28 days | 100 | CRP, WBC | Blood culture | -Newborns with clinically suspected neonatal sepsis in the NICU between April 2009 and March 2010 | -Neonates who were critically ill<br>-Severe jaundice due to blood group incompatibilities | Level 4 |
| Khan F. *J Coll Physicians Surg Pak*. 2019.[60] | NICU | Cross sectional | Pakistan | 0-28 days | 385 | CRP | Blood culture | - Inclusion criteria were neonates from 0 to 28 days of life having clinical features suggestive of NS and willingness of parents to participate in the study | - Excluded patients were those who were advised antibiotics (for any reason) 24 hours before admission to neonatal unit, those positive blood cultures which showed contamination and unwillingness of parents to participate in study. | Level 2 |
| Khashabi J, et al. *Iran J Med Sci.* 2004.[61] | NICU | Prospective cohort | Iran, Islamic Rep. | 0-13 days | 110 | CRP | Blood culture | -Newborns with suspected clinical sepsis defined by signs and symptoms suggestive of clinical sepsis including unexplained unstable temperature (hypo- and hyperthermia), lethargy, irritability, poor feeding or milk intolerance, vomiting, abdominal distension, bloody stool, respiratory dysfunction evidenced by apnea, tachypnea (>60 breaths/min); cardiovascular dysfunction such as persistent tachycardia (>160 beat/min) or bradycardia (<100 beat/min), seizure, sclerema<br>-biochemical and hematological parameters including persistent acidosis, unexplained hypo- and hyperglycemia, thrombocytopenia, leukopenia or leukocytosis | -Newborns who had undergone mechanical ventilation, surgical operation, exchange transfusion, or were resuscitated before admission<br>-Newborns with metabolic aberrations, chromosomal abnormalities, and who had received parenteral antibiotic therapy before admission, birth weight less than 2,000gm | Level 1 |
| Kiser C, et al. | NICU | Retrospective | United | Birth | 554 | CRP | Blood culture | -All neonates of gestational age | -None | Level 1 |

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| *Pediatrics*. 2014.[62] | | cohort | States of America | | | | | ≥35 weeks exposed to chorioamnionitis and admitted to level III NICU. | | |
| Kocabas E, et al. *Turk J Pediatr*. 2007.[63] | NICU and outpatient department | Prospective Cohort | Turkey | 1-30 days | 55 | CRP, PCT | Blood culture | -Consecutive neonates admitted with a suspected clinical sepsis and hospitalized<br>-Consecutive healthy neonates who had no signs of infection but were hospitalized for perinatal risk factors<br>-Consecutive healthy neonates without infectious risk factors admitted to well-baby outpatient clinics | -Newborns started on antibiotic treatment<br>-Newborns with a history of maternal antibiotic administration | Level 2 |
| Koksal N, et al. *Turk J Pediatr*. 2007.[64] | NICU | Prospective Cohort | Turkey | 0-30 days | 67 | CRP, PCT | Clinical criteria (including culture) | -Infants with clinical (Temperature instability, apnea, need for supplemented oxygen, need for ventilation, tachycardia/bradycardia, hypotension, feeding intolerance, abdominal distension, necrotizing enterocolitis) or laboratory findings of neonatal sepsis<br>-Infants who had no signs of clinical and laboratory infection were included as the control group | -Administration of antibiotic therapy during admission<br>-Lack of parental consent<br>-Newborns who died during follow-up<br>-Newborns who had exchange transfusion for neonatal hyperbilirubinemia | Level 5 |
| Kordek A, et al. *Postepy Hig Med Dosw (Online)*. 2014.[65] | NICU | Prospective cohort study | Poland | 5-50 days | 140 | CRP, PCT, WBC | Blood culture | -Clinically evidenced sepsis after three days of life.<br>-All cases fulfilled the Centers for Disease Control and Prevention (CDC) criteria for nosocomial infection. | NA | Level 3 |
| Koskenvuo et al. *Eur J Clin Microbiol Infect Dis*. 2003.[66] | NICU | Retrospective cohort | Finland | 0-84 hours | 22 | CRP, PCT | Blood culture | -Neonates admitted with clinical signs of infection | -Not specified | Level 3 |
| Krishna BV, et al. *Indian J Pathol Microbiol*. 2000.[67] | NICU | Prospective cohort | India | 0-28 days | 57 | CRP | Blood culture | -Neonates clinically suspected to have sepsis not otherwise specified | -None listed | Level 2 |
| Kumar D, et al. *Int J Pharm Clin Res*. 2021.[68] | NICU | Prospective cohort | India | 0-6 days | 80 | CRP | Blood culture | -age <7 days of life, inborn or outborn with suspected sepsis and with high risk factors (antenatal, natal, postnatal) | -age >7 days of life<br>-septic shock patients or rapidly deteriorating clinical condition | Level 3 |
| Kumar R, et al. *East Afr Med J*. 2010.[69] | NICU | Cross sectional | Kenya | 1-55 days | 212 | CRP | Blood culture | -All neonates admitted to KNH Newborn Unit during the study period with suspected sepsis | -Neonates whose parents/guardians declined to give consent and those with history of meconium aspiration, | Level 1 |

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| | | | | | | | | based on perinatal risk factors or suspicious clinical findings were recruited before first-line or change over to second-line were initiated. | perinatal asphyxia, tissue injury and severe hepatocellular involvement were excluded. | |
| Kumar S, et al. *Int J Pharma Clin Res*. 2022.[70] | NICU | Prospective Cohort | India | 0-28 days | 61 | CRP | Blood culture | All neonates (<28 days) presenting with symptoms and signs of sepsis like poor feeding, lethargy, tachypnea, hypothermia, convulsion, etc. were included in the study. | All newborns with neonatal hyperbilirubinemia due to causes other than sepsis like physiological jaundice, Rh, ABO incompatibility, TTN, MAS without clinical or laboratory suspicion of sepsis were excluded from the study. | Level 3 |
| Lam HS, et al. *Neonatology*. 2011.[71] | NICU | Prospective Cohort | Hong Kong | 0-30 days | 310 | CRP | Blood culture | -All infants admitted to NICU at Prince of Wales Hospital who presented with symptoms suggestive of intra-abdominal sepsis or surgical abdomen or<br>-Infants who required full sepsis screening and antibiotic treatment or<br>-Infants referred for pediatric surgical assessment | -Chromosomal abnormalities<br>-Lethal congenital malformations<br>-Family history of immunodeficiencies | Level 1 |
| Lopez Sastre JB, et al. *BMC Pediatr*. 2007.[72] | NICU | Prospective Cohort | Spain | 0-48 hours | 238 | PCT | Clinical criteria (including culture) | -All consecutive neonates admitted to participating hospital within 48 HOL who had blood samples available for timed PCT measurement according to three postnatal periods: shortly after birth, within 12-24 h of life, and within 36-48 h of age | -Infants born to mothers with gestational diabetes<br>-Refusal of parental consent for blood sampling | Level 4 |
| Lubis BM. *Int Med J*. 2021.[73] | NICU | Cross sectional | Indonesia | 0-28 days | 65 | PCT | Blood culture | -age <28 days admitted to perinatology ward and they were not suspected or proven with immunodeficiency, hematological disorder, or receiving immunomodulator drugs | -suspected or proven with immunodeficiency<br>-hematological disorder<br>-receiving immunomodulator drugs | Level 4 |
| Mannan MA, et al. *Mymensingh Med J*. 2010.[74] | NICU | Prospective cohort | Bangladesh | 0-28 days | 150 | CRP, WBC | Blood culture (42/100 were pre-treated) | -Newborns with one clinical feature (respiratory distress, poor feeding, lethargy, hypothermia, abdominal distention, sclerema, convulsion) AND one major or two minor risk factors (major risk factors were rupture of membranes > 24 hours, chorioamnionitis, maternal fever >100.4, Fetal HR >160) (minor risk factors: rupture of membranes >12 hours, maternal WBC >15,000, low Apgar, preterm labor, low birth weight, foul | -Newborns with any congenital abnormality | Level 3 |

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| | | | | | | | | lochia, maternal colonization) | | |
| Manucha V, et al. *J Paediatr Child Health.* 2002.[75] | NICU | Prospective cohort | India | 0-3 days | 150 | CRP | Blood culture | -Neonates clinically suspected to have sepsis based on abnormal fetal and maternal clinical findings "as described in standard textbooks of neonatology" | -None listed | Level 3 |
| Mathers NJ, et al. *Eur J Pediatr.* 1987.[76] | NICU | Prospective cohort | Germany | 0-27 days | 245 | CRP | Blood culture | -Consecutive admissions to the NICU | -Focal bacterial source (skin or UTI or gastrointestinal) | Level 1 |
| Milcent K, et al. *JAMA Pediatr.* 2016.[77] | Emergency Department | Prospective Cohort | France | 7-90 days | 2047 | CRP, PCT | -Blood, CSF, urine, stool culture (SBI)<br>-IBI defined as positive blood or CSF culture | Infants older than 7 days and younger than 91 days with temperatures of 38°C or higher at home or on admission | -antibiotics in previous 48 hours<br>-major comorbidities (immune deficiency, congenital abnormality, chronic disease)<br>-parental consent or data collection could not be obtained | Level 1 |
| Misra PK, et al. *Indian Pediatr.* 1989.[78] | NICU | Prospective cohort | India | 0-7 days | 83 | ESR, WBC | Blood culture | -Clinical manifestation of sepsis fever, hypothermia, poor suck, lethargy, sclerema | None listed | Level 5 |
| Mkony MF, et al. *BMC Pediatrics*. 2014.[79] | NICU | Prospective cohort | Tanzania | 0-28 days | 208 | CRP | Blood culture | -WHO clinical criteria history of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate ≥ 60 breaths per minute, severe chest indrawing, axillary temperature ≥ 37.5°C, axillary temperature ≤ 35.5°C, bulging anterior fontanelle, signs of infection on the skin with pus spots and umbilicus pus spots | -Unwillingness of the parent or guardian to participate in the study<br>-Very sick neonates in decompensated state and requiring resuscitation<br>-Neonates with severe congenital malformation | Level 1 |
| Mondal SK, et al. *Int J Appl Basic Med Res.* 2012.[80] | NICU | Prospective cohort | India | 0-30 days | 102 | CRP, ESR, WBC | Blood culture | -Clinical history, signs, symptoms, and presence of predisposing factors in mothers and neonates for sepsis.[1] | -None listed | Level 3 |
| Monsef A, et al. *Iran J Pediatr.* 2012.[81] | NICU | Cross sectional | Iran, Islamic Rep. | Not specified | 49 | PCT | Blood culture | -Newborns with clinical and laboratory findings in favor of bacterial infection (before antibiotic therapy) and a positive blood, CSF, or urine culture | -Newborns with prior antibiotic therapy, expired infants, exchange transfusion, direct or hemolytic hyperbilirubinemia | Level 2 |
| Morad EA, et al. *Int J Microbiol*. 2020.[82] | NICU | Cross sectional | Egypt, Arab Rep. | 1-16 days | 50 | CRP, PCT | Blood culture | - Any neonate (up to age 28 days) with signs or symptoms of suspected sepsis at the time of admission or who developed sepsis in the hospital during the study period was enrolled in this study. The suggestive clinical manifestation included respiratory distress, apnea, pallor, poor feeding, hypotension, shock, | - Any neonate with apparent major congenital anomalies, Apgar score less than seven, or on antibiotics therapy before the start of the study was excluded. | Level 2 |

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| | | | | | | | | instability of the temperature, lethargy, irritability, and increased oxygen requirement, besides abnormal laboratory findings as abnormal leukocyte count, increased I/T (immature to total neutrophil) ratio, and decreased platelet count. | | |
| Nakamura H, et al. *Acta Paediatr Jpn.* 1989.[83] | NICU | Prospective cohort | Japan | 0-100 days | 90 | CRP | Blood culture | -Infants admitted to NICU who were clinically suspected to have bacterial infection | -Not specified | Level 2 |
| Ng PC, et al. *Pediatr Res.* 2002.[84] | NICU | Prospective Cohort | Hong Kong | 0 days-1 year | 90 | CRP | Blood culture | -Birth weight <1500g<br>-Postnatal age >72h<br>-Symptoms suggestive of systemic infection and requiring full sepsis evaluation and antibiotic treatment<br>-Parental consent | -Baby of diabetic mother | Level 2 |
| Ng PC, et al. *Arch Dis Child Fetal Neonatal Ed*. 1997.[85] | NICU | Prospective Cohort | Hong Kong | 72 hours | 101 | CRP | Blood culture | - Preterm infants with (*a*) birth weight < 1500 g, (*b*) postnatal age > 72 hours, (*c*) sign and symptoms suggestive of systemic infection and requiring full sepsis evaluation and antibiotic treatment, and (*c*) parental consent, in the neonatal unit at Prince of Wales Hospital, Hong Kong were eligible for enroll-ment into the study. | - Patients who were already on parenteral antibiotic treatment at the time of sepsis evaluation, or had severe congenital or chromosomal abnormalities, were excluded. | Level 4 |
| Numbenjapon N, et al. *J Med Assoc Thai.* 2015.[86] | NICU | Prospective cohort | Thailand | Day of life 0 | 98 | CRP | Blood culture | -All neonates with birth weight > 1500 grams who were diagnosed as clinical sepsis defined as a neonate who had at least one of the following conditions: 1) maternal fever that required antibiotic treatment, 2) maternal prolonged rupture of membranes >24 hours, 3) purulent gastric content that contained more than 10 white blood cells per high power field, 4) fetal distress in utero, 5) clinical manifestation of sepsis including lethargy, irritability, poor feeding, core temperature higher than 37.5°C, tachycardia or bradycardia, respiratory distress, apnea, vomiting, hepatosplenomegaly, hypotonia, convulsion, poor skin | -Neonates who were intubated, had umbilical or central line catheterization, diagnosed with conditions requiring prolonged antibiotic treatment (e.g. meningitis, arthritis, and osteomyelitis) | Level 5 |

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| Nupponen I, et al. *Pediatrics.* 2001.[87] | NICU | Prospective Cohort | Finland | 0-48 hours | 47 | CRP | Blood culture; clinical criteria | -The series consisted of 39 neonates, with a gestational age of 29 to 41 weeks, who were treated in the neonatal unit for suspected infection. Inclusion criteria were the presence of at least 1 clinical sign suggesting infection at the age of 0 to 48 hours, and a blood sample for bacterial culture having been requested by the clinician.<br>- 12 healthy term neonates w/physiologic hyperbilirubinemia not requiring PTX and with normal CRP served as controls | -Plasma IL-8 concentration or neutrophil CD11b expression value missing. | Level 3 |
| Ohlin A, et al. *Acta Paediatr.* 2010.[88] | NICU | Prospective cohort | Sweden | 0-28 days | 393 | CRP | Blood culture | -All neonates who had clinical signs of infection and subsequent blood culture and sepsis treatment with IV antibiotics as determined by treating neonatologist | -Not stated | Level 1 |
| Omar J, et al. *Malays J Med Sci.* 2019.[89] | ICU | Prospective cohort | Malaysia | 24-120 hours | 60 | PCT | Blood culture | -Suspected neonatal sepsis due to either preterm ruptured of membrane or prolonged ruptured of membrane, maternal infection, chorioamnionitis, group B streptococcus colonization, or signs of fetal distress during labor.<br>-Neonates with feeding intolerance, lethargy or tachypnea, poor perfusion, seizures, respiratory distress, bradycardia, abdominal distention, or vomiting | -All neonates whose parents refused to consent | Level 2 |
| Pastor Peidró JA, et al. *An Pediatr.* 2007.[90] | NICU | Prospective cohort | Spain | 1 hour-30 days | 113 | PCT | Blood culture | -All newborns whose clinical history contained at least one risk factor for infection including bacteriuria during pregnancy, >18 hours of membrane rupture, and mothers received incomplete prophylactic antibiotics | -Not specified | Level 2 |
| Peakman M, et al. *Arch Dis Child.* 1992.[91] | NICU | Prospective Cohort | United Kingdom | 1-73 days | 56 | WBC | Blood, CSF, urine culture | - babies admitted to NICU<br>- either suspected of infection or controls (infants not suspected of infection but with blood taken for management purposes) | Not specified | Level 2 |
| Philip AGS, et al. *Pediatrics.* 1980.[92] | NICU | Prospective Cohort | United States of America | 0-7 days | 376 | CRP, WBC, ESR | Blood, CSF, urine culture | Any baby suspected on clinical grounds of having sepsis or meningitis in the first week after | Not specified | Level 1 |

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| | | | | | | | | birth was included in the study. | | |
| Pynn JM, et al. *Pediatr Res*. 2015.[93] | NICU | Prospective cohort | United States | >72 hours | 139 | CRP | Blood culture | - The eligible infants were of any GA and BW, inborn or outborn, who underwent one or more evaluations for late-onset sepsis. | - The infants on antibiotics at the time of sepsis evaluation were excluded. | Level 1 |
| Rashwan NI, et al. *Pediatr Neonatol*. 2019.[94] | NICU | Prospective Cohort | Egypt, Arab Rep. | Not specified (presumably 0-30 days based on enrollment of "neonates") | 168 | CRP, PCT | Blood culture | -Neonates recruited from the NICU who exhibited clinical signs and symptoms of sepsis (respiratory distress, apnea, oxygen dependence, feeding intolerance, poor feeding, hypotension, shock, poor peripheral perfusion, tachycardia, lethargy, temperature instability, seizures, altered mental status, skin mottling and unexplained acidosis) | -Clearly apparent malformations<br>-Prematurity<br>-Apgar score less than seven<br>-On antibiotics treatment before the start of the study | Level 1 |
| Resch B, et al. *Acta Paediatr*. 2003.[95] | NICU | Prospective Cohort | Austria | 0-12 hours | 68 | CRP, PCT | Blood culture; clinical criteria | -Positive clinical signs of sepsis and/or a history of factors associated with increased risk for infection | -Congenital malformations<br>-Congenital infections associated with the TORCH complex<br>-Refusal of parental consent | Level 2 |
| Rohsiswatmo R, et al. *J Neonatal Perinatal Med*. 2020.[96] | NICU | Cross sectional | Indonesia | 3-64 days | 52 | CRP, PCT, WBC | Blood culture | -Neonates >72 hours of age, at least one risk factor of LONS, and a predicted LONS score of >7<br>-Risk factors of LONS: low birth weight, prolonged parenteral nutrition, central intravenous access, and presence of morbidities (persistent ductus arteriosus, necrotizing enterocolitis, or hypoxic-ischemic encephalopathy) | -Multiple congenital anomalies or syndromes, history of surgery, or birth weight <1,000 grams | Level 2 |
| Russell GAB, et al. *Arch Dis Child.*. 1992.[97] | NICU | Prospective cohort | United Kingdom | Not specified | 172 | CRP | Blood culture | -All neonates admitted with either suspected infection or management of prematurity, low birth weight, respiratory distress syndrome, and asphyxia neonatorum | -Not stated | Level 2 |
| Saboohi E, et al. *Pak J Med Sci.* 2019.[98] | NICU | Prospective cohort | Pakistan | 0-7 days | 85 | CRP | Blood culture | -Neonates admitted to the NICU with presumed sepsis based on clinical suspicion not otherwise specified | -None listed | Level 3 |
| Sakha K, et al. *Pak J Biol Sci.* 2008.[99] | NICU | Retrospective cohort | Iran, Islamic Rep. | 0-28 days | 117 | CRP, PCT | Blood culture | -Neonates with suspected sepsis (proven sepsis who had positive blood culture and suspected sepsis who had negative blood culture but had positive CRP and either | -All neonates with congenital anomalies, gestational age <34 weeks, suspected hemorrhage, and neonates delivered with asphyxia. | Level 3 |

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| | | | | | | | | neutropenia or thrombocytopenia and positive chest x-ray) | | |
| Saleeh A, et al. *J Clin Neonatol*. 2020.[100] | NICU | Cross sectional | Egypt, Arab Rep. | 0-8 days | 55 | CRP | Clinical sepsis | -Preterm and full-term neonates with both sexes, diagnosed with neonatal sepsis based on clinical and laboratory results.<br><br>-We used clinical (temperature instability, respiratory rate >60 breaths/min plus grunting or desaturations, heart rate 180 beats/min or 100 beats/min, lethargy/altered mental status, glucose intolerance (plasma glucose >10 mmol/l) and feed intolerance) and laboratory criteria (thrombocytopenia, leukopenia, leukocytosis, CRP >10 mg/l or 2 standard deviation above normal value, immature neutrophils >10%, immature: total neutrophil ratio >0.2) plus positive blood cultures for diagnosis of neonatal sepsis. | -We excluded neonates with central nervous system malformations, birth asphyxia, and intracranial hemorrhages. | Level 4 |
| Salzer HR, et al. *Acta Obstet Gynecol Scand.* 1987.[101] | Not specified | Prospective cohort | Austria | Birth | 25 | CRP | Blood culture | -Infants whose mothers presented either with premature rupture of membranes alone, with PROM complicated by fever or without PROM but foul-smelling amniotic fluid and amnionitis (confirmed by histologic examination) | -Not stated | Level 3 |
| Schmidt BK, et al. *Ped Infect Dis J*. 1987.[102] | NICU | Prospective cohort | Canada | 4-48 days | 297 | CRP | Blood culture | -All neonates who underwent evaluation for suspected infection | -Not stated | Level 3 |
| Seibert K, et al. *J Paediatr Child Health*. 1990.[103] | Not specified | Prospective cohort | Australia | 0-3 days | 125 | CRP | Blood culture | -Neonates suspected of perinatally acquired infection, consisted of infants born at a gestational age of 31 weeks or less who were studied after birth. | -None listed | Level 3 |
| Sharma A, et al. *Indian J Pediatr*. 1993.[104] | NICU | Prospective cohort | India | 0-30 days | 50 | CRP, ESR | Blood culture | -Neonates with suspected sepsis with no obvious focus of infection | -None listed | Level 3 |
| Shaw CK, et al. *East J Med.* 2012.[105] | NICU | Retrospective Cohort | Nepal | 0-30 days | 183 | CRP | Blood culture or cerebrospinal fluid culture | -Neonates who presented with signs and symptoms of septicemia | Not specified | Level 3 |
| Sonawane VB, et al. *J* | Inpatient | Prospective cohort | India | 0-28 days | 108 | CRP, ESR, WBC | Blood culture | -Neonate with clinical suspicion of sepsis or with a positive | -None listed | Level 3 |

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| *Nepal Paediatr Soc*. 2014.[106] | | | | | | | | "Neonatal sepsis score" | | |
| Sorsa A. *Open Microbiol J*. 2018.[107] | NICU | Prospective Cohort | Ethiopia | 0-28 days | 303 | CRP, WBC | Blood culture | -Clinical dx of sepsis (≥2 of low birth weight (<2500 grams) or prematurity (<37 weeks of gestation), presence maternal febrile illness within 2 weeks prior to delivery, foul smelling and/or meconium stained amniotic liquid, suspected chorioamnionitis, rupture of membranes >18 hours, prolonged labor >24 hrs, perinatal asphyxia (Apgar score <4 at 1 minute), clinical signs of sepsis) | Neonate whose mother available was not to give consent and interview. | Level 3 |
| Squire EN, Jr., et al. *Pediatr Infect Dis J*. 1982.[108] | NICU | Prospective Cohort | United States of America | 0-30 days | 123 | CRP, ESR, WBC | Culture (blood, CSF, urine, tracheal aspirate, peritoneal fluid, and middle ear fluid) | -All newborns placed on antibiotics for presumptive bacterial infection | -Prior prophylactic antibiotics treatment<br>-Incomplete data | Level 3 |
| Stein M, et al. *Clin Pediatr*. 2015.[109] | Emergency Department | Prospective Cohort | Israel | 3 days-3 months | 112 | CRP, PCT, WBC | Blood, urine, CSF culture | -All children who were evaluated for suspected SBI for symptoms including body temperature ≥38.0C or ≤35.7C, vomiting, restlessness, drowsiness, poor appetite, pathologic jaundice, respiratory distress, or apnea | -Patients with underlying conditions<br>-Previous antibiotic treatment<br>-Immune deficiency<br>-Neonates with history of prematurity (born prior to 37 gestational weeks) | Level 2 |
| Steinberger E, et al. *Scan J Clin Lab Invest*. 2014.[110] | NICU | Retrospective Cohort | Austria | "Neonates", age not specified | 218 | CRP, PCT | Blood culture; clinical criteria | -Prematurity (<37 weeks of gestation)<br>-Suspected infection<br>-Inborn birth | -Death during the first 3 days of life<br>-Severe malformation<br>-Missing values of PCT, IL6 or CRP<br>-Unavailable information for the diagnosis of EOS | Level 2 |
| Sucilathangam G, et al. *J Clin Diagn Res*. 2012.[111] | NICU | Prospective Cohort | India | 0-24 days | 50 | CRP, ESR, PCT, WBC | Blood culture | -Neonates with signs suggestive of sepsis not otherwise specified | -Neonates who were on antibiotics previously<br>-Neonates who had birth asphyxia, aspiration syndromes, inborn errors of metabolism, and congenital anomalies | Level 3 |
| Tessema B, et al. *Diagnostics (Basel)*. 2020.[112] | Not specified | Cross sectional | Germany | 0-28 days | 739 | CRP | Blood culture | - Sepsis-suspected neonates were retrospectively classified as proven sepsis, clinical sepsis, or controls based on C-reactive protein (CRP) and blood culture results. Proven sepsis was defined as CRP > 10 mg/L in at least one of the five serial measurements and positive blood culture. Clinical sepsis was defined as | - Neonates with positive blood cultures for coagulase negative staphylococci (CoNS) organisms and CRP < 10 mg/L in all five serial measurements were considered as potential contamination and excluded from our analysis. | Level 3 |

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| | | | | | | | | CRP > 10 mg/L in at least one of the five serial measurements and negative blood culture. No sepsis (control) was defined as neonates suspected for sepsis, with negative blood culture, CRP < 10 mg/L in all five serial measurements, and neonates who had not started antibiotics treatment before blood collection. | | |
| Magudumana MO, et al. *J Trop Pediatr*. 2000.[113] | NICU | Prospective cohort | South Africa | 0-30 days | 255 | CRP | Blood culture | -All neonates who were investigated for suspected sepsis based on respiratory distress, apnea/bradycardia, lethargy, irritability, seizures, temperature instability, increasing vent requirements, hypotension, poor peripheral circulation, abdominal distention, and feeding intolerance | -Problem with specimen (e.g., insufficient sample, specimen lost)<br>-Lack of parental consent | Level 3 |
| Panda SK, et al. *Cureus*. 2021.[114] | NICU | Retrospective cohort | India | "neonates" | 93 | CRP | Blood culture | Not included | Not included | Level 5 |
| Puelloa Avila AC, et al. *Rev Chilena Infectol*. 2021.[115] | NICU | Cross sectional | Colombia | "neonates" | 198 | CRP | Blood culture | -neonates evaluated for sepsis | -born in another hospital, serious medical problems, low birth weight | Level 4 |
| Salah A, et al. *BMC Infect Dis*. 2021.[116] | NICU | Cross sectional | Yemen | 0-72 hours | 199 | CRP, WBC | Blood culture | -admitted for 72 hours or more | -congenital anomalies and hemolytic jaundice | Level 2 |
| Shivasharana B, et al. *Eur J Molecular Clin Med*. 2022.[117] | NICU | Prospective cohort | India | Not listed | 128 | PCT | Blood culture and clinical sepsis | -at least 3 symptoms and signs of late onset sepsis | -babies with clinical features of sepsis before 72 hours of life<br>-HIE stage III<br>-neonate with surgical problem<br>-babies with life threatening congenital anomalies<br>-extramural babies | Level 3 |
| Takassi OE, et al. *Arch Pediatr*. 2022.[118] | NICU | Case control | France | 0-3 days | 50 | CRP, PCT | Blood culture | -born alive at <37 weeks of gestational age with suspected neonatal bacterial infection during the first 3 days of life were included in the study | - | Level 2 |
| Tunç T, et al. *J Neonatal Perinatal Med*. 2020.[119] | NICU | Prospective cohort study | Turkey | 0-72 hours | 130 | CRP | Blood culture | -Preterm and term newborns being followed-up in the NICUs with the suspicion of sepsis<br>-Presenting with non-specific findings of sepsis including apnea, needing supplemental oxygen or mechanical ventilation | -Patients with congenital abnormalities | Level 3 |

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| | | | | | | | | hypotension, bradycardia or tachycardia, temperature instability, feeding intolerance, abdominal distension, and necrotizing enterocolitis | | |
| Turner D, et al. *Acta Paediatr.* 2006.[120] | NICU | Prospective Cohort | Israel | 3-66 days | 85 | CRP, PCT | Confirmed sepsis: positive blood, CSF or urine culture/radiologically proven pneumonia/cellulitis and clinical signs of infection. Clinical sepsis: clinical signs of infection | -Preterm infants (< 36 weeks) admitted to NICU<br>-Sepsis workup during admission | -No parental consent | Level 4 |
| Utkarshni SJ , et al. *Int J Curr Res Med Sci.* 2018[121] | NICU | Prospective cohort | India | 4-28 days | 50 | CRP, PCT | Blood culture | - Any neonate with signs and symptoms suggestive for sepsis or who developed signs of sepsis while in the ward in 4-28 days of life. | - The exclusion criteria for this study was administration of antibiotic therapy prior to admission, neonates with birth asphyxia, aspiration syndromes, laboratory findings, suggestive of inborn errors or metabolism and in neonates with any congenital anomalies. | Level 3 |
| Varsha, et al. *Indian J Pathol Microbiol.* 2003.[122] | NICU | Prospective Cohort | India | "Neonates" , age not specified | 150 | CRP, WBC | Blood culture | -Admitted to nursery with clinically suspected sepsis<br>-Term, appropriate for gestational age, apparently healthy neonates recruited as controls | -Pregnancy induced hypertension<br>-Birth asphyxia | Level 2 |
| Vazzalwar R, et al. *J Perinatol.* 2005.[123] | NICU | Prospective Cohort | United States of America | "Neonates" , age not specified | 51 | CRP, PCT | Blood, cerebrospinal, or urine culture | -<37 weeks gestation at birth<br>-Birth weight ≤1500 g<br>-No antibiotic therapy for the previous 48 hours | -Lethal congenital anomalies | Level 3 |
| Velasco R, et al. *Pediatr Infec Dis J.* 2015.[124] | Emergency Department | Prospective cohort | Spain | 0-90 days | 766 | CRP, PCT, WBC | Blood and/or CSF culture | -Neonates <90 days old presenting with fever without a source to the pediatric emergency department who had CRP, WBC count, urine dipstick, urine and blood culture performed | -No collection or urine or blood by sterile method<br>-No WBC or CRP values determined<br>-Patients in whom the history and/or the physical examination suggested the source of the fever<br>-Afebrile patients at arrival who had not any measured temperature >38°C at home<br>-Parental refusal to participate<br>-No phone contact to follow-up 1 month after the study | Level 2 |
| Verboon-Maciolek MA, et al. *Pediatric* | Multiple | Prospective Cohort | Netherlands | 0-60 days | 92 | CRP, PCT | Culture (blood, CSF), PCR | -Two or more of the following clinical symptoms: fever or temperature instability, | Not specified | Level 3 |

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| *Research.* 2006.[125] | | | | | | | | respiratory distress, poor peripheral circulation, irritability, lethargy, apnea, tachycardia, hypotension, poor feeding, abdominal distention, and diarrhea<br>-Controls were infants without signs of infection who were admitted to the NICU | | |
| Wagle S, et al. *J Paediatr Child Health.* 1994.[126] | NICU | Prospective Cohort | Australia | Age not specified | 309 | CRP, WBC | Culture (blood, cerebrospinal fluid, urine) | -All babies born <30 weeks GA admitted to the NICU between Jan to Dec 1990 in the state of Western Australia | Not specified | Level 2 |
| Waterfield T, et al. *BMC Pediatr.* 2018.[127] | Emergency Department | Prospective Cohort | United Kingdom | 0-90 days | 126 | CRP, PCT | Blood, CSF culture | -Any child under 90 days of age presenting with signs or symptoms suggestive of possible bacterial infection | Not specified | Level 1 |
| Weirich E, et al. *J Pediatr.* 1998.[128] | NICU | Prospective cohort | United States of America | 0-1 day | 106 | CRP | Blood, CSF, and urine cultures (bacterial or viral) | -All neonates born >28 weeks gestation admitted on the first day of life with perceived risk for infection, per attending pediatrician in accordance with NICU guidelines, either because of maternal intrapartum risk factors or infant symptoms | -Neonates with noninfectious diagnoses that accounted for symptoms | Level 3 |
| Wen N, et al. *Int J Clin Exp Med.* 2019.[129] | NICU | Prospective cohort | China | 1-28 days | 92 | CRP, PCT | Clinical "established by the Chinese Medical Association Pediatrics Branch" | -Patients admitted to the neonatology department from January to February 2018 were included | -Simultaneous infection with other blood disorders, autoimmune diseases, malignant tumor complications, and patients who were unwilling or unable to cooperate with the study and follow-up | Level 4 |
| West BA, et al. *Antimicrob Resist Infect Control.* 2012.[130] | NICU | Prospective cohort | Nigeria | "neonates" | 420 | CRP | Blood culture | -Neonates with clinical suspicion or risk factors for sepsis | -Neonates of mothers who had intrapartum antibiotics within 1 week of delivery<br>-Neonates with prior antibiotic therapy for present illness | Level 2 |
| Woelker JU, et al. *Pediatr Emerg Care.* 2012.[131] | Emergency Department | Prospective Cohort | United States of America | 2-60 days | 155 | PCT, WBC | Serious bacterial infection was defined as positive blood or CSF culture, bacterial pathogen in stool, or as a positive urine culture with greater than 50,000 colony- | -Infants presenting to the pediatric ED with a rectal temperature of 38-C or higher (recorded at home, in a physician's office, or in the pediatric ED) who appeared generally well | -Beyond study age<br>-No recorded temperature<br>-Temperature less than threshold<br>-Pretreatment with antibiotics | Level 1 |

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| | | | | | | | forming units/mL of a single pathogen or 10,000 to 49,000 colony-forming units/mL with positive urinalysis (UA) | | | |
| Ye Q, et al. *Pediatr Res*. 2017.[132] | Multiple | Prospective Cohort | China | 0-30 days | 840 | CRP | Blood culture | -positive blood culture and compatible clinical features, (respiratory distress, cyanosis, poor perfusion, lethargy, poor feeding, apnea, and bradycardia)<br>-Neonatal patients with jaundice or enterovirus infection and healthy newborns were matched for age, body weight, and gender and recruited as controls | Not specified | Level 3 |
| Yu R, et al. J Int Med Res. 2020.[133] | NICU | Prospective cohort | China | 0-28 days | 47 | PCT | Blood culture | -admitted neonates with clinically suspected sepsis<br>-criteria for sepsis included: 1) symptoms of infection, including an unstable temperature, apnea, or decrease in heart rate; and 2) positive for at least two of the following experimental tests: total white blood cell count <5 106/L or >20 106/L), immature-to-total neutrophil ratio 0.16, platelet count 100 106/L, CRP levels !6 mg/L, and PCT levels 0.5 ng/mL. | | Level 3 |
| Zhou B, et al. *Exp Ther Med*. 2016.[134] | NICU | Prospective cohort | China | day of life 0 | 200 | CRP | Blood culture | -Neonates with premature rupture of membranes, amnionitis, meconium stained amniotic fluid, birthweight <2,500 grams, preterm infants (<37 weeks), resuscitation required in the labor room, mother having temperature of >38C, urinary tract infection in the mother | -Neonates born to mothers who had received antenatal antibiotic therapy <48 hours prior to delivery<br>-Neonates with major congenital anomalies | Level 2 |

**Supplemental Table 2**. Test characteristics of erythrocyte sedimentation rate (ESR) in the diagnosis of neonatal sepsis.

| ESR Cut Point (mm/hour), ≥ | Sensitivity (95% CI) | Specificity (95% CI) | Youden's Index | Area Under Receiver Operating Characteristic Curve | Reference Standard(s) | Total Patients, n | Disease, n[a] | Studies, n | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| *All Included Studies* | | | | | | | | | |
| 15 | 0.30 (0.19, 0.44) | 0.81 (0.26, 0.98) | 0.11 | 0.36 (0.17, 0.85) | Blood culture | 599 | 125 | 3 | 29.7-30.3% |

[a]Defined as positive for disease using reference standard.

**Supplemental Table 3.** Test characteristics of white blood cell (WBC) count in the diagnosis of neonatal sepsis

| WBC Level (cells/mm$^3$), ≥ | Sensitivity (95% CI) | Specificity (95% CI) | Youden's Index | Area Under Receiver Operating Characteristic Curve | Reference Standard(s) | Total Patients, n | Disease, n[a] | Studies, n | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| *All Included Studies* | | | | | | | | | |
| 5,000 | 0.30 (0.21, 0.41) | 0.87 (0.83, 0.91) | 0.17 | 0.75 (0.47, 0.86) | Blood culture | 1,850 | 509 | 11 | 5.3% |
| *High Income Countries Only* | | | | | | | | | |

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| 5,000 | 0.35 (0.21, 0.52) | 0.86 (0.79, 0.91) | 0.21 | 0.73 (0.37, 0.87) | Blood culture | 1,280 | 292 | 5 | 8.1-8.2% |
| 15,000 | 0.34 (0.20, 0.52) | 0.74 (0.52, 0.88) | 0.08 | 0.50 (0.30, 0.77) | Blood culture | 973 | 79 | 3 | 0% |
| *Low Income Countries Only* | | | | | | | | | |
| 5,000 | 0.26 (0.14, 0.43) | 0.89 (0.82, 0.94) | 0.15 | 0.76 (0.38, 0.89) | Blood culture | 570 | 217 | 6 | 3.4% |
| 20,000 | 0.40 (0.15, 0.70) | 0.87 (0.73, 0.95) | 0.27 | 0.78 (0.38, 0.88) | Blood culture | 610 | 192 | 3 | 1.1% |

[a]Defined as positive for disease using reference standard.

**Appendix 1.** Search terms used to identify potential articles reporting the results of studies evaluating test characteristics of selected biomarkers.

PubMed

((((((((((Procalcitonin[mesh] OR Procalcitonin[tiab] OR Calcitonin[mesh] OR "Calcitonin Precursor Polyprotein"[tiab] OR "Calcitonin 1"[tiab] OR "Calcitonin Related Polypeptide Alpha"[tiab] OR "Pro-Calcitonin"[tiab])))) OR (("C-Reactive Protein"[mesh] OR "C Reactive Protein"[tiab] OR CRP[tiab]))) OR (("Blood Sedimentation"[mesh] OR "Blood Sedimentation"[tiab] OR "Erythrocyte Sedimentation"[tiab] OR ESR[tiab])))) AND (((((("Radiography, Thoracic"[mesh] OR "chest x ray"[tiab] OR "chest x rays"[tiab] OR CXR[tiab] OR "thoracic radiography"[tiab] OR "thoracic radiographies"[tiab] OR "chest radiography"[tiab] OR "chest radiographies"[tiab] OR "thoracic x ray"[tiab] OR "thoracic x rays"[tiab])) OR (("Bacteriological Techniques"[mesh] OR culture[tiab] OR cultures[tiab] OR cultured[tiab]))) OR (("clinical impression"[tiab] OR "clinical impressions"[tiab] OR "clinical gestalt"[tiab] OR "clinical presentation"[tiab] OR "clinical presentations"[tiab] OR "clinical feature"[tiab] OR "clinical features"[tiab] OR "clinical finding"[tiab] OR "clinical findings"[tiab])))))) AND (((((((((adolescent[mesh] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR youth[tiab] OR youths[tiab]))) OR ((child[mesh] OR child[tiab] OR children[tiab]))) OR (("child, preschool"[mesh] OR toddler[tiab] OR toddlers[tiab]))) OR ((infant[mesh] OR infants[tiab] OR infant[tiab] OR baby[tiab] OR babies[tiab]))) OR (("infant, newborn"[mesh] OR newborn[tiab] OR newborns[tiab] OR neonate[tiab] OR neonates[tiab]))) OR ((pediatrics[mesh] OR pediatrics[tiab] OR pediatric[tiab])))) NOT "case reports"[Publication Type]

EMBASE

('procalcitonin'/exp OR procalcitonin:ab,ti OR 'calcitonin'/exp OR 'calcitonin':ab,ti OR 'calcitonin precursor polyprotein':ab,ti OR 'calcitonin 1':ab,ti OR 'calcitonin related polypeptide alpha':ab,ti OR 'pro-calcitonin':ab,ti OR 'c reactive protein'/exp OR 'c reactive protein' OR 'c reactive protein':ab,ti OR crp:ab,ti OR 'erythrocyte sedimentation rate'/exp OR 'erythrocyte sedimentation rate' OR 'blood sedimentation':ab,ti OR 'erythrocyte sedimentation':ab,ti OR esr:ab,ti) AND ('thorax radiography'/exp OR 'chest x ray':ab,ti OR 'chest x rays':ab,ti OR cxr:ab,ti OR 'thoracic radiography':ab,ti OR 'thoracic radiographies':ab,ti OR 'chest radiography':ab,ti OR 'chest radiographies':ab,ti OR 'thoracic x ray':ab,ti OR 'thoracic x rays':ab,ti OR 'bacterium culture'/exp OR culture:ab,ti OR cultures:ab,ti OR cultured:ab,ti) AND ('adolescent'/exp OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR teen:ab,ti OR teens:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR youth:ab,ti OR youths:ab,ti OR 'child'/exp OR child:ab,ti OR children:ab,ti OR 'preschool child'/exp OR 'school child'/exp OR toddler:ab,ti OR toddlers:ab,ti OR 'infant'/exp OR 'baby'/exp OR infants:ab,ti OR infant:ab,ti OR baby:ab,ti OR babies:ab,ti OR 'newborn'/exp OR newborn:ab,ti OR newborns:ab,ti OR neonate:ab,ti OR neonates:ab,ti OR 'pediatrics'/exp OR pediatrics:ab,ti OR pediatric:ab,ti) NOT 'case report'/de

CINAHL

(DE ' Calcitonin' OR AB ‘procalcitonin’ OR AB 'calcitonin'/exp OR AB ‘calcitonin’ OR AB 'calcitonin precurs’ OR AB ‘polyprotein' OR AB 'calcitonin 1' OR AB 'calcitonin related polypeptide alpha' OR AB 'pro-calcitonin' OR DE ‘C-Reactive Protein’ OR AB 'c reactive protein' OR AB 'c reactive protein' OR AB ‘crp’ OR DE ‘Blood Sedimentation’ OR AB 'erythrocyte sedimentation rate' OR AB 'blood sedimentation' OR AB 'erythrocyte sedimentation' OR AB ‘esr’) AND (DE ‘Radiography, Thoracic’ OR AB 'chest x ray' OR AB 'chest x rays' OR AB ‘cxr’ OR AB 'thoracic radiography' OR AB 'thoracic radiographies' OR AB 'chest radiography' OR AB 'chest radiographies' OR AB 'thoracic x ray' OR AB 'thoracic x rays' OR DE Microbial Culture and Sensitivity Tests' OR AB ‘culture’ OR AB ‘cultures’ OR AB ‘cultured’) AND (DE 'adolescence' OR AB ‘adolescent’ OR AB ‘adolescents’ OR AB ‘adolescence’ OR AB ‘teen’ OR AB ‘teens’ OR AB ‘teenager’ OR AB ‘teenagers’ OR AB ‘youth’ OR AB ‘youths’ OR DE 'child' OR AB ‘child’ OR AB ‘children’ OR DE ‘child, preschool’ OR AB ‘toddler’ OR AB ‘toddlers’ OR DE 'infant' OR AB ‘infants’ OR AB ‘infant’ OR AB ‘baby’ OR AB ‘babies’ OR AB ‘newborn’ OR AB ‘newborns’ OR AB ‘neonate’ OR AB ‘neonates’ OR DE ‘pediatrics’ OR AB ‘pediatrics’ OR AB ‘pediatric’)

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