Accuracy of leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis: a critical review

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Authors' objectives
To evaluate the accuracy of C-reactive protein (CRP) and leukocyte indices in the diagnosis of infants suspected of having septicaemia in a neonatal intensive care setting.

Searching
EMBASE and MEDLINE were searched from 1988 and 1966, respectively, to May 1994 using the following search terms: 'infant', 'new-born', 'C-reactive protein', 'leukocyte count', and 'sepsis' or 'septicaemia' or 'infection'. The bibliographies of primary and review articles were also searched, as were the authors' personal files. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to study design were specified.

Specific interventions included in the review
Studies were included in the review if patients had a complete white blood cell count and differential and/or CRP measurement as part of a sepsis workup.

Reference standard test against which the new test was compared
Studies were included if an appropriate reference standard had been used: neonatal infection defined as a clinical condition compatible with systemic infection and (1) a positive culture from blood, cerebrospinal fluid, or urine obtained by suprapubic aspiration or clean catheterisation of the bladder, or (2) positive cultures of body fluids obtained from normally sterile sites, or (3) post-mortem histopathologic diagnosis of meningitis or pneumonia.

Participants included in the review
Studies of pre-term or term infants admitted to the intensive care unit and evaluated for sepsis were eligible for inclusion.

Outcomes assessed in the review
Studies were included only if they provided sufficient information to enable the construction of 2x2 tables. Sensitivity, specificity, and positive and negative predictive values were the outcome measures calculated by the review.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the studies for inclusion and any disagreements were resolved by consensus. Agreement about which studies to include in the overview was 92% with a weighted kappa of 0.76.

Assessment of study quality
The studies were reviewed and assigned a methodological criteria score. The score was based on the method of enrolment of neonates in the study, the quality of the laboratory assessment and the reference standard measures. All of the studies were reviewed by two independent reviewers. The final validity rating was reached by consensus.

Data extraction
The data were extracted by one reviewer and checked by a second. Any disagreements were resolved by consensus.
Methods of synthesis

How were the studies combined?
Due to the heterogeneity of the studies, a meta-analysis was not attempted. The results were reported individually for the included primary studies, along with a narrative summary.

How were differences between studies investigated?
Between-study homogeneity of true-positive and true-negative rates (sensitivity and specificity) were tested using the chi-squared test, or Fisher's exact test for small studies.

Results of the review

Sixteen studies involving 2,219 patients were included.

Significant between-study heterogeneity was found. For leukocyte rates the P value was 0.014. Similar results were obtained for studies that measured CRP using qualitative latex agglutination methods (P<0.01) and quantitative methods (P<0.001).

Fifteen of the 16 studies scored greater than 6 on a methodological quality scale of 3 to 9.

The leukocyte count and ratios had a wide range of sensitivities (17 to 90%) and specificities (31 to 100%). Qualitative CRP measurement gave sensitivities of 44 to 92% and specificities of 42 to 93%, whilst quantitative measurement gave sensitivities of 58 to 100% (5 of the studies recorded sensitivities of 100%) and specificities of 68 to 94%.

Authors' conclusions

Since a number of non-infectious factors can influence the neonatal leukocyte count, its usefulness as a screening tool for neonatal septicaemia is limited. Measuring CRP qualitatively was no more sensitive than simple leukocyte indices. CRP, though not perfect, is probably the best single diagnostic test available for the evaluation of neonates suspected of sepsis. Clinicians faced with a neonate with suspected sepsis cannot rely on either CRP or leukocyte indices alone to make a decision, given that the results vary significantly depending on the methods of measurement used and the target population.

CRD commentary

The review defined a clear research question in terms of well-described and appropriate inclusion criteria. The literature search presented was adequate, but included no attempt to identify unpublished studies, leaving the review open to the effects of publication bias. The review methodology was rigorous and well described, and a limited assessment of the methodological quality of the included studies was presented (although the quality data obtained were not used further in the review). Given the heterogeneity of the included studies, a narrative summary was reasonable; pooling the sensitivities and specificities from primary studies would have been inappropriate. However, alongside the assessment of threshold effects, the presentation of summary receiver operator characteristic curves could have provided a useful visualisation of the relationship between the sensitivity and specificity for each test. The authors discussed some potential reasons for the observed between-study heterogeneity, but did not provide sufficient detail for the reader to clearly define the characteristics of the individual included studies.

Implications of the review for practice and research

Practice: Clinicians faced with a neonate with suspected sepsis cannot rely on either CRP or leukocyte indices alone to make a decision, given that the results vary significantly depending on the methods of measurement used and the target population.

Research: The authors did not state any implications for further research.

Bibliographic details

**PubMedID**
7638010

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Biomarkers /blood; C-Reactive Protein /metabolism; Humans; Infant, Newborn; Intensive Care, Neonatal; Leukocyte Count; Sensitivity and Specificity; Sepsis /blood /diagnosis

**AccessionNumber**
11995001325

**Date bibliographic record published**
30/11/2003

**Date abstract record published**
30/11/2003

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.