Beyond the complete blood cell count and C-reactive protein: a systematic review of modern diagnostic tests for neonatal sepsis

CRD summary
This review assessed the accuracy of modern laboratory tests in diagnosing serious bacterial infection in newborns. The authors concluded that few diagnostic tests have been evaluated in good-quality studies and that there was insufficient evidence to support the use of these tests in routine clinical practice. These conclusions are likely to be reliable.

Authors' objectives
To assess the accuracy of modern laboratory tests in diagnosing serious bacterial infection in newborns.

Searching
PubMed, EMBASE and the Cochrane Controlled Trials Register were searched for studies published in the English language from 1995 through 2001; the MeSH terms were stated. The reference lists in reviews were also checked.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not explicitly defined in terms of study design. The use of the keyword 'diagnosis' implied that diagnostic studies were sought.

Specific interventions included in the review
Studies of 'new' laboratory tests (excluding haematological tests and acute phase C-reactive protein) that focused on serious bacterial infections were eligible for inclusion. The specific tests used in the included studies were: interleukin-6, interleukin-8, interleukin-1 receptor antagonist, tumour necrosis factor (TNF)-alpha, fibronectin levels, neutrophil elastase inhibitor level, neutrophil CD11B level, polymerase chain reaction, procalcitonin level, TNF-receptor p55 and p75 levels, and soluble intracellular adhesion molecule level. Some studies used a combination of more than one test.

Reference standard test against which the new test was compared
The studies had to compare new tests with proven serious bacterial infections diagnosed using standard criteria. Only studies that used unequivocal proof of bacterial infection (bacterial growth) in cultures from central nervous system fluid, or blood from sterile sites, were included. Studies of clinical sepsis (defined as not meeting criteria for infection), urinary tract infections and studies of antenatal tests were excluded. Studies reporting ante- and postnatal infection were only included if they presented separate data for neonatal patients. The included studies used different cut-off values to diagnose the presence of infection. The review used the authors' own cut-off values where these were reported.

Participants included in the review
Studies of newborns with a postnatal age of less than 90 days were eligible for inclusion. The included studies were of infants with gestational age (where reported) ranging from 23 to 44 weeks

Outcomes assessed in the review
The inclusion criteria were not specified in terms of outcomes. The outcomes measured in the included studies were the sensitivity, specificity, and positive and negative likelihood ratios (LRs).

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion and resolved any disagreements through discussion with a third reviewer. The kappa statistic was used to assess inter-reviewer agreement.
Assessment of study quality
Validity was assessed by examining whether the studies distinguished true bacterial infection from clinical sepsis and discussing other aspects of validity (e.g., adequacy of description of the population and study size). Two reviewers independently assessed validity and resolved any disagreements through discussion with a third reviewer.

Data extraction
Two reviewers independently extracted data from each study to calculate the sensitivity, specificity and LRs for each test. Attempts were made to obtain further information from authors of reports with missing data. Where possible, the reviewers created 2x2 tables and calculated the sensitivity, specificity and LRs, together with their respective 95% confidence intervals (CIs) and positive and negative predictive values. Where it was not possible to calculate the LRs from raw data, the reviewers calculated the LRs from sensitivity and specificity values provided in the original reports.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative under the headings of cut-off values and performance of the test.

How were differences between studies investigated?
The results were reported separately for studies that presented adequate data to allow the reviewers to independently calculate diagnostic accuracy statistics; for studies with LRs greater than 10; and for studies with LRs greater than 10, as calculated using raw data.

Results of the review
Thirty-seven studies met the inclusion criteria. Seventeen studies that were assessed as distinguishing bacterial infection from clinical sepsis were included in the review (299 septic infants).

Seven studies (68 infants) presented sufficient raw data to enable the reviewers to calculate the sensitivity, specificity and LRs, along with CIs. For the other 10 studies, the reviewers used the values presented by the authors.

The most commonly reported test was the interleukin-6 level test (7 studies with 92 septic and 524 non septic infants). The other tests were assessed by 3 studies or less.

The sensitivity and specificity values (reported and calculated) varied widely: sensitivity ranged from 57 to 100% and specificity from 43 to 100%. Positive LRs ranged from 1.5 to infinity.

Six tests reported in 8 studies had LRs greater than 10. The reviewers independently calculated an LR greater than 10 for procalcitonin (1 study), neutrophil CD11b (2 studies), interleukin-8 (1 study). The LR was greater than 10 for two of the 3 studies of procalcitonin.

Three studies used combinations of tests, but none of these studies presented sufficient data to allow an independent calculation of diagnostic accuracy statistics. All were small studies (the largest had 26 septic infants) and none reported LRs greater than 10.

Authors' conclusions
Few diagnostic tests had been evaluated in good-quality studies. There was insufficient evidence to support the use of these tests in routine clinical practice.

CRD commentary
The review question was clear in terms of the participants, diagnostic tests and reference test. The inclusion criteria were not explicitly stated in terms of the outcomes or study design. Several relevant sources were searched and the search terms were stated. By limiting the included studies to those published in the English language, some relevant
studies might have been omitted. No attempt was made to locate unpublished studies, thus raising the possibility of publication bias. Two reviewers independently selected the studies, assessed validity and extracted the data, which reduces the potential for bias and errors. Validity was not formally assessed using criteria appropriate for diagnostic studies, although some methodological limitations in the individual studies were discussed in the text.

Some information on the included studies was presented in tabular format. The narrative synthesis was appropriate given the small number of studies. The authors attempted to calculate diagnostic accuracy statistics from raw data, and reported the results separately for studies in which this was possible. Some of the limitations of the review were discussed in the text. The evidence presented appears to support the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that the tests should not be used in routine clinical practice.

Research: The authors stated that adequately powered, well-conducted studies are required to evaluate the diagnostic accuracy of these new tests.

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