The accuracy of the procalcitonin test for the diagnosis of neonatal sepsis: a meta-analysis
Yu Z, Liu J, Sun Q, Qiu Y, Han S, Guo X

CRD summary
This review concluded that the procalcitonin test was a valuable additional tool for diagnosis of neonatal sepsis, showing moderate accuracy for this diagnosis and better accuracy than the C-reactive protein test in the diagnosis of late-onset neonatal sepsis. Limitations of the review, analyses and included studies mean the conclusion should be treated with some caution.

Authors' objectives
To assess the accuracy of the procalcitonin test for diagnosing neonatal sepsis.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched without language restrictions from 1996 to May 2009; search terms were reported. Reference lists of included studies and review articles were searched.

Study selection
Diagnostic accuracy studies that evaluated the procalcitonin test for diagnosis of neonatal sepsis were eligible for inclusion.

Most studies were in babies who were pre-term in the neonatal intensive care unit and/or at risk of sepsis. Where controls were used, these were non-infected full-term or premature newborns. Sepsis was diagnosed by culture in all studies; most studies also used clinical signs and symptoms. Procalcitonin was most commonly determined using quantitative immunoluminometric assay or semi-quantitative immunochromatographic assay. Timing of the procalcitonin test varied across studies, from at birth (using umbilical blood) to over 72 hours after birth. Cut-off for a positive test ranged from 0.5ng/mL to 100ng/mL; higher cut-offs were generally used at 24 and 48 hours after birth compared with at birth, 24 hours and over 72 hours.

Two reviewers independently selected studies for the review; disagreements were resolved by discussion or referral to a third reviewer.

Assessment of study quality
Study quality was assessed using an 11-point version of the QUADAS tool

The authors did not state how many reviewers assessed study quality.

Data extraction
Data were extracted to construct 2x2 tables of test performance from which sensitivity, specificity and diagnostic odds ratio, with 95% confidence intervals (CI), were calculated. Early-onset sepsis was defined as diagnosis up to 48 hours post birth and late-onset as diagnosis at 72 hours of age or over. When studies reported results for a range of cut-off points, data were extracted for the cut off with the best efficiency value ((true positive+true negative)/total number of cases). Study authors were contacted for missing data.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Pooled estimates of the diagnostic measures, with 95% CI, were calculated: a fixed-effect method was used where heterogeneity was considered not to be statistically significant (p<0.05); otherwise a random-effects model was used. Heterogeneity was investigated using Cochran's Q and I². Summary receiver operating characteristic curves (SROC) were produced using the Moses-Littenberg model. Studies were grouped by diagnostic criteria for sepsis and timing of the procalcitonin test.

Subgroup analyses were conducted to investigate the impact of different cut-offs, presence of risk factors for sepsis and
timing of the test. Sensitivity analyses were conducted to investigate the impact of individual studies considered to be different in design or population.

**Results of the review**
Twenty-two studies met the inclusion criteria (2,836 newborns, range 55 to 286). The major methodological limitations of the included studies were identified as a lack of blinding of interpreters of the index test and reference standard, explanation of withdrawals, reporting of uninterpretable results and disease progression bias. Studies performed better with regards avoided partial and differential verification bias and incorporation bias and recruiting a representative patients sample, but the graphic showed that several studies still failed these criteria.

**Early onset sepsis:** When using umbilical blood (three studies), procalcitonin test sensitivity was 78% (95% CI 68% to 86%) and specificity was 83% (95% CI 80% to 86%). For blood samples taken at zero to 12 hours (eight studies) sensitivity was 77% (95% CI 72% to 81%) and specificity was 87% (95% CI 84% to 90%). At 12 to 24 hours (four studies) sensitivity was 77% (95% CI 68% to 84%) and specificity was 89% (95% CI 85% to 91%). At 24 to 48 hours (six studies) sensitivity was 70% (95% CI 64% to 75%) and specificity was 88% (95% CI 85% to 91%).

**Late-onset sepsis (>72 hours):** Where sepsis was proven or suspected (seven studies), sensitivity was 62% (95% CI 57% to 67%) and specificity was 92% (95% CI 89% to 95%). Where sepsis was proven (eight studies), sensitivity was 82% (95% CI 77% to 86%) and specificity was 77% (95% CI 73% to 80%).

Considerable heterogeneity was observed for most analyses; where heterogeneity was considered to be absent, this was using \( p<0.05 \). Results were reported that compared the diagnostic outcomes of the procalcitonin test to those of the C-reactive protein test; sensitivity was higher for the procalcitonin test, but the results for specificity differed depending on whether the comparisons were conducted in the same patients or not. The diagnostic odds ratio and results of further subgroup and sensitivity analyses were reported.

**Authors' conclusions**
The procalcitonin test showed moderate accuracy in diagnosing neonatal sepsis, regardless of differences in diagnostic criteria and time points for testing. For diagnosis of late-onset neonatal sepsis, the procalcitonin test showed better accuracy than the C-reactive protein test. The procalcitonin test was a valuable additional tool for diagnosis of neonatal sepsis.

**CRD commentary**
The authors addressed a clear research question supported by broad but appropriate inclusion criteria. Several relevant sources were searched. Studies in languages other than English were included, which reduced potential for language bias. No specific attempts were made to locate unpublished studies, so publication bias could not be ruled out. Study selection was conducted in duplicate; it was unclear whether similar methods to reduce error and bias were employed during data extraction and assessment of study quality.

Appropriate criteria were used to assess study quality; only summary results were presented, so it was impossible to determine which studies that were prone to methodological weaknesses contributed to individual analyses. There seemed to be some discrepancies between text, figures and tables. It appeared that results of the assessment of heterogeneity were reported only for analyses of diagnostic odds ratios. The methods used to produce the pooled estimates of diagnostic accuracy had limitations. The SROC model used did not account for heterogeneity across the studies and more robust models were available.

Limitations of the review, analyses and included studies mean the conclusion should be treated with some caution.

**Implications of the review for practice and research**
**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that an adequately powered trial was needed to investigate the findings of the review further, particularly the testing of umbilical cord blood.

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