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C-reactive protein unlikely to be accurate for early diagnosis of late-onset infection in newborn infants

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Clinical question

Is serum C-reactive protein (CRP) measurement at initial evaluation useful to diagnose late-onset infection in newborn infants?

Context

Newborn infants, especially those who are unwell or preterm, are at risk of developing severe infections (such as bloodstream infections) during their stay on neonatal units. Late-onset infections occur at least 72 hours after birth and are difficult to diagnose early. The current standard test to confirm this diagnosis, positive microbiological culture, takes about 24 to 48 hours. A delayed treatment increases the morbidity and mortality of late-onset infections. Therefore, clinicians are using additional tests in the hope of identifying infants with infection earlier and being able to optimally target early treatment. An example is measuring the blood level of CRP, which takes about 1 hour and has become common practice in neonatal units. It remains unknown, however, if this test at initial evaluation in infants with signs of possible late-onset infection is actually accurate to make the diagnosis.

To correctly assess the usefulness (accuracy) of the CRP test, studies should recruit newborn infants that are suspected to have a late-onset infection. These infants should be tested twice: first using the new test (CRP) followed by the standard test (blood culture). Results can then be compared: how many infants with an infection have a positive CRP test (true positive), and how many infants without an infection indeed have a normal CRP (true negative). Alternatively, it would be important to know how many infants would be falsely diagnosed, i.e. infants with infection having a negative CRP (false negatives) as well as infants without infection having an elevated CRP (false positives). The analysis determines the optimal value between sensitivity of the test (the ability of the test to correctly diagnose infants with an infection) and the specificity (the ability of the test to correctly identify infants who do not have an infection).

The review describes 20 studies including a total number of 1615 newborn infants, which stayed in the hospital for at least 72 hours after birth. Most were small, single-centre, prospective cohort studies conducted in neonatal units in high- or middle-income countries since the late 1990s. The authors used the threshold for the CRP test as defined by individual studies (expected typically to be in the range of 5 mg/L to 10 mg/L). The prevalence of late-onset infection in the included studies

ranged from 20% to 82% (median of 40%). The authors applied the results of the meta-analyses to a hypothetical cohort of 1000 neonates with a prevalence of infection of 20%, 40%, or 60%.

Summary of the results

Sensitivity and specificity are related: At median reported specificity (0.74), sensitivity was 0.62 (95% CI 0.50 to 0.73); at the lower quartile reported specificity (0.61), sensitivity was 0.76 (95% CI 0.65 to 0.84); at the upper quartile reported specificity (0.85), sensitivity was 0.44 (95% CI 0.32 to 0.57).

The results varied between studies, but it was not possible to assess whether results depended on gestational age, types of infection, or types of infecting micro-organism mostly because no subgroup data were available. Whether the studies used a predefined threshold or not, and whether studies used a standard threshold of between 5 mg/L and 10 mg/L or not, did not explain the variation between the studies.

What happens when we apply these results to a hypothetical group of 1000 newborn infants that are about to be evaluated for possible late-onset infection?

Results vary based on the prevalence of infection, therefore the authors estimated results in three situations. If the prevalence of true infection is 40% (which was the median prevalence in the included studies), then, on average, 152 cases of infection would be missed (false negative) and 156 non-infected infants would be wrongly diagnosed with an infection (false positive).

Table: Results of the meta-analysis applied to a hypothetical cohort of 1000 newborns in three situations: infection prevalence 20%, 40% and 60%.

Infection	Prevalence 20%		Prevalence 40%		Prevalence 60%	
	Positive culture	Negative culture	Positive culture	Negative culture	Positive culture	Negative culture
Positive CRP	124	208	248	156	372	104
Negative CRP	76	592	152	444	228	396
	200	800	400	600	600	400

Remarks

Certainty of evidence was moderate. Risk of bias in the included studies was generally low. Studies avoided inappropriate exclusion of infants. The serum CRP level was measured in infants presenting with clinical features of late-onset infection before the results of the reference standard were known. Most (13/20) studies prespecified a threshold of CRP level consistent with current clinical practice (5 mg/L to 12 mg/L). All studies used blood samples taken at the initial investigation of each infant to determine the serum CRP level and for the blood culture. Due to the nature of the reference standard, the blood culture results followed 24 to 48 hours after the index test, depending on laboratory procedure. Across all studies, there was a low risk that the patient flow might have introduced bias.

Conclusion:

Measuring the blood level of CRP as an additional triage test for late-onset infection in newborn infants is not sufficiently accurate to determine which infant should receive treatment with antimicrobial agents or further testing.

Implications for practice:

CRP measurement at initial evaluation of an infant with suspected late-onset infection does not aid early diagnosis and is not likely to be considered a sufficiently accurate test to select infants who would undergo further investigation or who should be treated with antimicrobial therapy or other interventions.

REFERENCE:

Brown JVE, Meader N, Cleminson J, McGuire W. C-reactive protein for diagnosing late-onset infection in newborn infants. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No.: CD012126. DOI: 10.1002/14651858.CD012126.pub2.

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^ **CI:** confidence interval