Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review

CRD summary
This review concluded that measuring inflammatory markers can be useful for diagnosing serious infections in febrile children in ambulatory settings. Measuring white blood cell count was less useful for ruling in serious infection and not useful for ruling out serious infection. This tentative conclusion is likely to be reliable, although possibility of publication bias should be borne in mind.

Authors' objectives
To assess the diagnostic value of laboratory tests for the diagnosis of serious infections in febrile children in ambulatory settings.

Searching
MEDLINE, EMBASE, DARE and CINAHL were searched without language restrictions. No time restrictions were imposed. A first search was performed in October 2008 and an update was performed in June 2009. Search terms were reported. Reference lists of included studies, systematic reviews and relevant guidelines were screened. Experts were contacted to identify additional relevant studies.

Study selection
Studies that evaluated the accuracy of clinical features or laboratory tests for diagnosis of serious infections in previously well children and adolescents (aged one month to 18 years) who presented to ambulatory care in Europe, Canada, USA, Australia, New Zealand and Japan were eligible for inclusion. Ambulatory care was defined as general or family practice, paediatric outpatient clinics, paediatric assessment units and emergency departments. Serious infections were defined as sepsis (including bacteraemia), meningitis, pneumonia, osteomyelitis, cellulitis, gastroenteritis with dehydration, complicated urinary tract infections and viral respiratory tract infections complicated by hypoxia. Studies restricted to one specific serious infection (bacteraemia or meningitis) were excluded. Only studies that reported sufficient data to enable construction of 2x2 tables were included.

The included studies assessed various laboratory tests that included white blood cell count, C reactive protein, procalcitonin, band count, interleukins, absolute neutrophil count, erythrocyte sedimentation rate and left shift. Cut-off values for each test were reported. Most of the included studies were conducted in emergency departments. All studies recruited patients on the presence of fever. Prevalence of serious infections ranged from 4.5% to 29.3%. Patient age ranged from under three months to 16 years. Reference standards were blood culture for bacteraemia, cerebrospinal fluid analysis and culture for meningitis, chest radiography for pneumonia, urine culture with/without dimercaptosuccinic acid scan for urinary tract infections and blood culture with/without clinical features for sepsis. There were two UK studies.

Two reviewers independently assessed studies for inclusion. Any discrepancies were resolved by a third reviewer.

Assessment of study quality
Study quality was assessed with QUADAS criteria. Study quality was classified into A, B, C and D. Studies that fulfilled all QUADAS criteria were classed as A. Studies were classed as C if there was no independent reference standard, with interpretation of reference standard unblinded to results of the index feature or with an excessively long period between recording of the index feature and outcome. Studies were classed as D if there was no or unclear total verification with reference standard or with interpretation of the index feature unblinded to results of the reference standard. All other studies were classed as B.

Two reviewers independently performed validity assessment. Any disagreements were resolved by consensus or in consultation with study authors for clarification where necessary.
**Data extraction**

Data were extracted to populate 2x2 contingency tables (numbers of true positive, false negative, false positive and true negative test results) to enable calculation of positive and negative likelihood ratios with 95% confidence intervals (CIs) calculated on the standard error of a proportion. Where there was an empty cell in the 2x2 table, the authors added 0.5 to the cell to calculate likelihood ratios. Study authors were contacted for additional data where necessary.

Data were extracted by one reviewer and checked by a second.

**Methods of synthesis**

Studies were combined in a meta-analysis using bivariate random-effects models if at least four studies were available for a particular laboratory test; otherwise, studies were combined in a narrative synthesis. Pooled estimates of positive and negative likelihood ratios and their 95% CIs were calculated. Summary receiver operating characteristic (ROC) curves were constructed for studies with multiple thresholds. For C reactive protein and procalcitonin, data from studies that reported sensitivity and specificity at multiple thresholds were pooled using the bivariate method of Dukic and Gatsonis. Pooling of results for white blood cell count was not possible due to heterogeneity.

**Results of the review**

Fourteen diagnostic cohort studies were included in the review (n=3,981 participants). Study quality was modest. No studies received an A rating. One study was rated B. Six studies were rated C. Seven studies were rated D. Ten studies reported using consecutive enrolment.

**C reactive protein (five studies):** The pooled positive likelihood ratio was 3.15 (95% CI 2.67 to 3.71; five studies) and the pooled negative likelihood ratio was 0.33 (95% CI 0.22 to 0.49; five studies) across all cut-off values.

**White blood cell count (seven studies):** White blood cell indicators were less valuable than inflammatory markers for ruling in serious infection. The positive likelihood ratio ranged from 0.87 to 2.43. The negative likelihood ratio ranged from 0.61 to 1.14, which indicated no value for ruling out serious infection.

**Band count (three studies):** The positive likelihood ratio ranged from 1.45 to 3.05 and the negative likelihood ratio ranged from 0.65 to 0.97.

**Procalcitonin (three studies):** The positive likelihood ratio ranged from 1.75 to 3.11 and the negative likelihood ratio ranged from 0.08 to 0.35.

**Interleukins (two studies):** The positive likelihood ratio ranged from 1.89 to 2.74 and the negative likelihood ratio ranged from 0.33 to 0.77.

**Absolute neutrophil count (two studies):** The positive likelihood ratio ranged from 1.06 to 1.38 and the negative likelihood ratio ranged from 0.90 to 0.93.

The best performing clinical decision rule was testing urinalysis in combination with C reactive protein and procalcitonin, with a positive likelihood ratio of 4.92 (95% CI 3.26 to 7.43) and a negative likelihood ratio of 0.07 (95% CI 0.02 to 0.27).

Summary ROC curves showed that the shape of curves for C reactive protein and procalcitonin were generally similar and the confidence intervals largely overlapped, which indicated comparable diagnostic accuracy. Most data points for white blood cell count lay close to the centre of the plot, which indicated limited diagnostic value.

Only one included study assessed left shift test or erythrocyte sedimentation rate. Further results were reported.

**Authors’ conclusions**

Measuring inflammatory markers can be useful for the diagnosis of serious infections in febrile children in ambulatory settings. Measuring white blood cell count was less useful for ruling in serious infection and not useful for ruling out
serious infection.

**CRD commentary**
The review addressed a clear question. Inclusion criteria were defined. Relevant databases were searched. Efforts were made to find published studies. There was no apparent search for unpublished studies, which risked publication bias. There was no reported assessment of publication bias. No language restrictions were applied to the search, which minimised the risk of language bias. Sufficient attempts were made to minimise biases and errors at all stages of the review process. Appropriate criteria were used to assess study quality. Appropriate methods were used to analyse data and pool results, with the aid of relevant graphical displays. Restriction of the review to studies conducted in developed countries and largely in emergency settings limited the generalisability of findings.

The review was generally well-conducted. The authors’ tentative conclusion reflected the evidence presented, as relatively low positive likelihood ratios suggested that the evidence was not strong. The conclusion is likely to be reliable, although the possibility of publication bias should be borne in mind.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians should apply different cut-off values to rule in or rule out serious infection when measuring inflammatory markers for the diagnosis of serious infections in febrile children.

**Research:** The authors stated that more rigorous studies (including studies in primary care) were required to assess the value of laboratory tests (ideally at point of care) alongside clinical diagnostic measurements including vital signs. Future research should evaluate the cost-effectiveness of different diagnostic strategies.

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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.