Value of Acute Phase Reactants in the Diagnosis of Pediatric Infections

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Objective

To evaluate the utility of acute phase reactants (ESR, CRP, procalcitonin) in the diagnosis of pediatric infections.

Strategy:

Systematic Review / Meta-analysis
Evidence-based Review
Landmark Articles
Acute Phase Reactants

Heterogenous group of plasma proteins that increase or decrease in response to inflammatory stimuli such as infections, trauma, acute arthritis, systemic autoimmune disorders and neoplasms.
ESR and CRP: most commonly used

Procalcitonin: increasing evidence to support its usefulness as a marker in bacterial infections
**Acute Phase Reactants:**

**TRADITIONAL USES:**
- Markers of inflammation
- Measure of sickness index

**Potential Wider Roles:**
- Early diagnosis
- Infectious vs noninfectious
- Prognostic marker
- Antibiotic guidance strategy

**Long-term Favorable Impact on:**
- Antibiotic Stewardship
- Antibiotic Resistance

**More judicious antibiotic prescriptions**
OUTLINE OF DISCUSSION

❖ Overview of Acute Phase Reactants
❖ Acute Phase Reactants as …….
  ▪ Guide to ID Diagnosis
  ▪ Guide to Antibiotic Use
❖ Implications for Practice
❖ Implications for Research
**Erythrocyte Sedimentation Rate**

- Measures the distance that a vertical column of anticoagulated blood has fallen in one hour.
- Value in diagnosis of infection remains unclear.
- Any condition that affects RBC or fibrinogen alters the value of ESR.
- Rises within 24–48 hours.
- Falls back slowly with resolution.
C-REACTIVE PROTEIN

- Better measure of an acute-phase response
- More sensitive to subtle changes in the acute-phase response
- Produced by the liver in response to cytokines, mainly IL-6.
- Normal CRP level: < 10 mg/L.

- Rises after 12–24 hours
- Peaks within 2–3 days
PROCALCITONIN

- Peptide prehormone of calcitonin
- Normal serum concentration: <0.05 ng/ml
- Bacterial infections: PCT is stimulated by cytokines IL-1, IL-6, and TNF α
- Viral infections: PCT is downgraded by γ-interferon
- Detectable: 3–4 hours
- Peak: 6–24 hours
OUTLINE OF DISCUSSION

- Overview of Acute Phase Reactants
- Acute Phase Reactants as .......
  - Guide to ID Diagnosis
  - Guide to Antibiotic Use
- Implications for Practice
- Implications for Research
Utility of the ESR: Key Considerations

- Simple and inexpensive test of chronic inflammatory activity.
- Limited by its low sensitivity and specificity.
- ESR >100 mm/hr: infection, malignancy or temporal arteritis.
- Little value in the diagnosis of osteomyelitis, but when elevated, it can be of clinical significance to monitor response to therapy.

Median and IQR of Biomarkers in Patients with pneumonic and non-pneumonic LRTI


CRP is more discriminant than ESR in differentiating pneumonia and other ALRTI.
ROC Curve of CRP, ESR and other Immunologic Markers
Pneumonia vs Other ALRTI

CRP: AUC = 0.93 (95% CI 0.89-0.96, p<0.0001).
CRP is a useful adjunct in differentiating pneumonia from OALRTI.

CRP is neither sufficiently sensitive to rule out nor sufficiently specific to rule in an infiltrate and bacterial etiology of LRTI.

Accuracy is low during the early phase of infection.

A normal initial CRP is not sufficient to justify withholding antibiotics.

Serial determinations 24 to 48 hours after the onset of symptoms improves diagnostic accuracy.

A growing body of evidence suggests a link between gestational age and CRP kinetics with lower CRP values and lower CRP response to infection in preterm compared to term newborns.

CRP undergoes a physiologic 3-day-rise after birth

Non-infectious confounders: meconium aspiration syndrome.
Procalcitonin and CRP as markers for bacterial infections vs noninfective causes of inflammation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Procalcitonin markers</th>
<th>C-reactive protein markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of results</td>
<td>Sensitivity, % (95% CI)</td>
</tr>
<tr>
<td></td>
<td>TP/FN</td>
<td>FP/TN</td>
</tr>
<tr>
<td>Aouifi et al.</td>
<td>46/2</td>
<td>8/41</td>
</tr>
<tr>
<td>Enguix et al.</td>
<td>19/3</td>
<td>1/23</td>
</tr>
<tr>
<td>Hatherill et al.</td>
<td>103/3</td>
<td>9/40</td>
</tr>
<tr>
<td>Muller</td>
<td>52/3</td>
<td>6/40</td>
</tr>
<tr>
<td>Penel et al.</td>
<td>43/14</td>
<td>0/5</td>
</tr>
<tr>
<td>Rothenburger et al.</td>
<td>12/2</td>
<td>3/42</td>
</tr>
<tr>
<td>Selberg et al.</td>
<td>19/5</td>
<td>3/6</td>
</tr>
<tr>
<td>Suprin et al.</td>
<td>49/6</td>
<td>26/14</td>
</tr>
<tr>
<td>Ugarte et al.</td>
<td>75/31</td>
<td>36/48</td>
</tr>
<tr>
<td>Viallon et al.</td>
<td>19/2</td>
<td>2/38</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE: FN, false negative; FP, false positive; TN, true negative, TP, true positive.

sROC curves comparing procalcitonin and C-reactive protein as markers for detection of bacterial infections vs noninfective causes of inflammation.

Procalcitonin and CRP as markers for bacterial versus viral infections.

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<thead>
<tr>
<th>Study</th>
<th>No. of results</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
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<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TP/FN</td>
<td>FP/TN</td>
<td></td>
<td>TP/FN</td>
<td>FP/TN</td>
<td></td>
</tr>
<tr>
<td>Hatherill et al.</td>
<td>103/6</td>
<td>9/8</td>
<td>94 (88–98)</td>
<td>73/2</td>
<td>36/12</td>
<td>97 (90–100)</td>
</tr>
<tr>
<td>Lorrot et al.</td>
<td>126/16</td>
<td>36/258</td>
<td>89 (82–93)</td>
<td>122/30</td>
<td>40/244</td>
<td>80 (73–86)</td>
</tr>
<tr>
<td>Schwarz et al.</td>
<td>11/0</td>
<td>5/14</td>
<td>100 (72–100)</td>
<td>14/6</td>
<td>1/8</td>
<td>70 (46–87)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>...</td>
<td>...</td>
<td><strong>92 (86–95)</strong></td>
<td>...</td>
<td>...</td>
<td><strong>86 (65–95)</strong></td>
</tr>
</tbody>
</table>

**NOTE.** FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Procalcitonin and C-reactive protein levels as markers for bacterial versus viral infections

<table>
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<tr>
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<th>PCT</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q value (95% CI)</td>
<td>89% (82%–96%)</td>
<td>83% (81%–85%)</td>
</tr>
<tr>
<td>Positive Likelihood ratio (95% CI)</td>
<td>6.05 (4.67-7.82)</td>
<td>3.75 (3.06-4.59)</td>
</tr>
<tr>
<td>Negative Likelihood ratio (95% CI)</td>
<td>0.10 (0.06–0.15)</td>
<td>0.20 (0.15–0.27)</td>
</tr>
</tbody>
</table>

The diagnostic accuracy of PCT is higher than CRP among hospitalized patients with suspected bacterial infections.

Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

Christina Wacker, Anna Prkno, Frank M Brunkhorst*, Peter Schlattmann*

Summary

Background Procalcitonin is a promising marker for identification of bacterial infections. We assessed the accuracy and clinical value of procalcitonin for diagnosis of sepsis in critically ill patients.

Methods We searched Medline, Embase, ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct, from inception to Feb 21, 2012, and reference lists of identified primary studies. We included articles written in English, German, or French that investigated procalcitonin for differentiation of septic patients—those with sepsis, severe sepsis, or septic shock—from those with a systemic inflammatory response syndrome of non-infectious origin. Studies of healthy people, patients without probable infection, and children younger than 28 days were excluded. Two independent investigators extracted patient and study characteristics; discrepancies were resolved by consensus. We calculated individual and pooled sensitivities and specificities. We used I² to test heterogeneity and investigated the source of heterogeneity by metaregression.

Findings Our search returned 3487 reports, of which 30 fulfilled the inclusion criteria, accounting for 3244 patients. Bivariate analysis yielded a mean sensitivity of 0.77 (95% CI 0.72–0.81) and specificity of 0.79 (95% CI 0.74–0.84). The area under the receiver operating characteristic curve was 0.85 (95% CI 0.81–0.88). The studies had substantial heterogeneity (I²=96%, 95% CI 94–99). None of the subgroups investigated—population, admission category, assay used, severity of disease, and description and masking of the reference standard—could account for the heterogeneity.

Interpretation Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients. Nevertheless, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment.
Procalcitonin is a helpful biomarker for early diagnosis of sepsis. Nevertheless, the results of the test must be interpreted carefully in the context of medical history, PE and microbiological assessment.

### Acute Phase Reactants in Specific Infections

<table>
<thead>
<tr>
<th>Clinical Infection</th>
<th>Acute Phase Reactant</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>ESR&gt;50</td>
<td>Higher predictive value of duration of hospital stay</td>
</tr>
<tr>
<td></td>
<td>CRP&gt;70</td>
<td></td>
</tr>
<tr>
<td>Skin and Soft Tissue Infection</td>
<td>CRP&gt;150</td>
<td>Higher likelihood of Necrotizing SSTI</td>
</tr>
<tr>
<td>Infective Endocarditis</td>
<td>CRP&gt;122</td>
<td>Predictors of poor outcome</td>
</tr>
<tr>
<td></td>
<td>PCT&gt;0.5</td>
<td>PCT is a better marker for IE than CRP (SV 0.81; SP 0.85)</td>
</tr>
<tr>
<td>UTI</td>
<td>PCT&gt;0.5</td>
<td>High likelihood of pyelonephritis and renal scar in children with UTI</td>
</tr>
</tbody>
</table>

ESR, CRP and Procalcitonin in the diagnosis of Acute Pyelonephritis in Children

ESR > 30mm/hr
CRP > 20mg/ml
PCT > 0.5ng/ml

ESR, CRP, PCT do not appear to be sufficiently accurate in differentiating children with cystitis from those with pyelonephritis.

Shaikh et.al. Procalcitonin, CRP and ESR for the diagnosis of Acute Pyelonephritis in Children (Systematic Review) 2015 The Cochrane Collaboration. Published by John Wiley and Sons, Ltd.
OUTLINE OF DISCUSSION

- Overview of Acute Phase Reactants

  - Acute Phase Reactants as……...
    - Guide to ID Diagnosis
    - Guide to Antibiotic Use: ARI, Sepsis

- Implications for Practice

- Implications for Research
# CRP Guidance in Respiratory Infections

<table>
<thead>
<tr>
<th>CRP value</th>
<th>Interpretation</th>
<th>Guide to antibiotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Pneumonia extremely unlikely</td>
<td>Discourage antibiotic</td>
</tr>
<tr>
<td>20-50</td>
<td>Pneumonia very unlikely</td>
<td>Consider delayed prescribing</td>
</tr>
<tr>
<td>51-100</td>
<td>Possible pneumonia</td>
<td>Consider delayed prescribing</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>Severe infection</td>
<td>Prescribe antibiotics immediately</td>
</tr>
<tr>
<td></td>
<td>Pneumonia very likely</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>Comparative Risk</th>
<th>Effect R.R.(95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of antibiotic prescriptions</td>
<td>IRCT 519/1000</td>
<td>0.90 (0.8-1.02)</td>
<td>1309 (3)</td>
<td>Moderate</td>
</tr>
<tr>
<td>CRCT 525/1000</td>
<td>467/1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>357/1000</td>
<td>0.68 (0.61-0.75)</td>
<td></td>
<td>1975 (3)</td>
<td></td>
</tr>
<tr>
<td>Clinical Recovery (7days)</td>
<td>414/1000</td>
<td>1.03 (0.93-1.14)</td>
<td>1264 (3)</td>
<td>Moderate</td>
</tr>
<tr>
<td>426/1000</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

# Procalcitonin Guidance in Respiratory Infections

<table>
<thead>
<tr>
<th>PCT value</th>
<th>Guide to antibiotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.10</td>
<td>Strongly discourage antibiotic</td>
</tr>
<tr>
<td>&lt; 0.25</td>
<td>Discourage antibiotic</td>
</tr>
<tr>
<td>&gt; 0.25</td>
<td>Encourage antibiotic</td>
</tr>
<tr>
<td>&gt; 0.50</td>
<td>Strongly encourage antibiotic</td>
</tr>
</tbody>
</table>

### PROCALCITONIN ALGORITHM COMPARED TO STANDARD CARE FOR GUIDING ANTIBIOTIC THERAPY IN ARI

**Population:** Patients with ARI  
**Settings:** Primary Care, ER, ICU  
**Intervention:** Procalcitonin algorithm  
**Comparison:** Standard care

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>Comparative Risk</th>
<th>Relative Effect O.R. (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Care</td>
<td>Procalcitonin algorithm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>60/1000</td>
<td>58/1000</td>
<td>0.91 (0.7-1.19)</td>
<td>4211 (14)</td>
</tr>
<tr>
<td><strong>Treatment Failure</strong></td>
<td>219/1000</td>
<td>189/1000</td>
<td>0.83 (0.71-0.97)</td>
<td>4211 (14)</td>
</tr>
<tr>
<td><strong>Antibiotic exposure (mean)</strong></td>
<td>8 days</td>
<td>3.47 days</td>
<td></td>
<td>4211 (14)</td>
</tr>
</tbody>
</table>

Schuetz et al. Procalcitonin to initiate or discontinue antibiotics in ARI (Review)  
2012 The Cochrane Collaboration. Published by John Wiley and Sons, Ltd.
**PROCALCITONIN GUIDANCE FOR SUSPECTED SEPSIS**

In all unstable patients, initiate antibiotics immediately.

<table>
<thead>
<tr>
<th>PCT Value (ng/mL)</th>
<th>Interpretation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 – 0.5</td>
<td>Low likelihood for sepsis</td>
<td>Antibiotic discouraged</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>Increased likelihood for sepsis</td>
<td>Antibiotic encouraged</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>High risk of sepsis/ septic shock</td>
<td>Antibiotic strongly encouraged</td>
</tr>
</tbody>
</table>

PCT GUIDANCE FOR SUSPECTED SEPSIS: THE PRORATA TRIAL

PCT GUIDANCE FOR SUSPECTED SEPSIS: THE PRORATA TRIAL

Evidence suggests that PCT guidance in ICUs decreases overall antibiotic use and has no significant effect on mortality and morbidity (based on length of hospital stay).

Proportion of newborns treated with antibiotics:
Standard group (82%); PCT group (55%)
Absolute risk reduction 27%; OR 0.27 (95% CI 0.12–0.62)

Clinical outcome was similar and favorable in both groups.

**Conclusion**: PCT guidance shortens the duration of antibiotic therapy in infants with suspected early-onset sepsis.

OUTLINE OF DISCUSSION

- Overview of Acute Phase Reactants
- Acute Phase Reactants as
  - Guide to ID Diagnosis
  - Guide to Antibiotic Use
- Implications for Practice – ARI, Sepsis
- Implications for Research
• Acute-phase reactants (ESR, CRP, PCT) cannot be used as the sole determinant to distinguish between viral and bacterial causes of CAP. (Strong recommendation; High-quality evidence)

• Acute-phase reactants need not be routinely measured in fully immunized children with CAP who are managed as outpatients. (Strong recommendation; Low-quality evidence)

• In patients with serious disease, APRs may be used in conjunction with clinical findings to assess response to therapy. (Weak recommendation; Low-quality evidence)
Avoiding routine use of antibiotics in the baby

Do not routinely give antibiotics to babies without risk factors for infection or clinical indicators or laboratory evidence of possible infection.

Investigations before starting antibiotics in the baby

When starting antibiotics in babies with risk factors for infection or clinical indicators of possible infection, perform a blood culture before administering the first dose.

Measure CRP at presentation when starting antibiotics in babies with risk factors for infection or clinical indicators of possible infection.

Neonatal infection: Antibiotics for Prevention and Treatment.
NICE Clinical guideline: 22 August 2012
Duration of antibiotic treatment:

- In babies already given antibiotics, do CRP 18–24 hours after presentation.

- In babies given antibiotics, consider stopping the antibiotics at 36 hours if:
  - the blood culture is negative, and
  - the initial clinical suspicion of infection was not strong, and
  - the clinical condition is reassuring with no indicators of possible infection
  - the levels and trends of CRP are reassuring.

Neonatal infection: Antibiotics for Prevention and Treatment. NICE Clinical guideline: 22 August 2012
CRP is accepted as a useful test for ruling out an infection, monitoring treatment response and guiding duration of antibiotic therapy.
A diagnosis of sepsis should be based on infection, documented or suspected, plus some of the following criteria:

1. General variables: T > 38.3°C or below 36°C; HR > 90 /minute; rapid breathing; altered mental status; significant edema; and ↑ blood sugar in the absence of diabetes.

2. Inflammatory variables: ↓↑ WBC or >10% stabs; ↑CRP; ↑PCT.

3. Haemodynamic and tissue perfusion variables: ↓BP; and ↑lactate

4. Organ dysfunction variables: ↓PaO2; ↓urine output; ↑creatinine; coagulation abnormalities; absent bowel sounds; ↓platelets; and ↑ plasma bilirubin.

Guideline Statements....SEPSIS

Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012
Procalcitonin testing for diagnosing and monitoring sepsis. NICE diagnostics guidance. October 2015
Implications for Research

1. Role of APRs in diagnosing IDs in immunosuppressed patients.

2. Comparison of APR guidance with other antibiotic-saving strategies.


4. Multicenter trials involving heterogeneous patient groups to assess the effect of APR guidance on patient morbidity, mortality, antimicrobial stewardship and drug resistance.
As a guide to ID diagnosis…

- ESR has limited value in ID diagnosis but helpful in monitoring treatment response.

- CRP is a useful adjunct in differentiating pneumonia from other ALRTI.

- In neonatal sepsis, CRP is more accurate if done serially.

- PCT is a more accurate marker for bacterial infections than CRP.

- PCT is a helpful marker for sepsis. However, it must be interpreted within the context of a careful history, PE and other labs.

- CPGs on ARI and Sepsis acknowledge the importance of APRs in disease diagnosis and management.
As guide to antibiotic use…

- In ARI:
  - CRP guidance reduces antibiotic use with no effect on recovery and duration of illness.
  - PCT guidance reduces antibiotic use with no increase in mortality or hospital stay.

- In sepsis:
  - Serial CRP is useful in the management of neonatal sepsis.
  - PCT guidance decreases antibiotic use with no ill effect on patient outcome.

Decisions on antibiotic use should not be based solely on APRs.
Diagnosis is not the end, but the beginning of practice.

~Martín H. Fischer (1879–1962)

Thank You