Procalcitonin-
Early-Warning System

Irwin Reiss, MD PhD
Professor of Neonatology
Head, Division of Neonatology
Erasmus MC, Rotterdam
i.reiss@erasmusmc.nl

ORIGINAL ARTICLE

Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study

Weiss et al. AJCM 2015

Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013
Shefali Gai, Joy E. Lawn, Daniel R. Hogan, Colin Mathers, & Simon N. Cousens

High-mortality model

Proportion of neonatal deaths

0-6 days 0-27 days

Peren. Important Congen. Sepsis Pneumonia Intestinal Resusc. Other

World Health Organ 2015:93:19-28
Neurodevelopmental and Growth Impairment Among Extremely Low-Birth-Weight Infants With Neonatal Infection

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Uninfected</th>
<th>Clinical Infection</th>
<th>Septic Alarms</th>
<th>Septic + NEC</th>
<th>NEC</th>
<th>Sepsis Plus NEC</th>
<th>Neonatal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME &lt; 1000</td>
<td>320/1000 (32%)</td>
<td>125/1000 (13%)</td>
<td>90/1000 (9%)</td>
<td>60/1000 (6%)</td>
<td>30/1000 (3%)</td>
<td>15/1000 (1%)</td>
<td>10/1000 (1%)</td>
</tr>
<tr>
<td>PDI &lt; 20</td>
<td>250/1000 (25%)</td>
<td>125/1000 (13%)</td>
<td>90/1000 (9%)</td>
<td>60/1000 (6%)</td>
<td>30/1000 (3%)</td>
<td>15/1000 (1%)</td>
<td>10/1000 (1%)</td>
</tr>
<tr>
<td>PI</td>
<td>150/1000 (15%)</td>
<td>75/1000 (7%)</td>
<td>50/1000 (5%)</td>
<td>30/1000 (3%)</td>
<td>15/1000 (1%)</td>
<td>7.5/1000 (0.7%)</td>
<td>5/1000 (0.5%)</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>110/1000 (11%)</td>
<td>55/1000 (5%)</td>
<td>35/1000 (3%)</td>
<td>20/1000 (2%)</td>
<td>10/1000 (1%)</td>
<td>5/1000 (0.5%)</td>
<td>2.5/1000 (0.25%)</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>90/1000 (9%)</td>
<td>45/1000 (4.5%)</td>
<td>20/1000 (2%)</td>
<td>10/1000 (1%)</td>
<td>5/1000 (0.5%)</td>
<td>2.5/1000 (0.25%)</td>
<td>1.25/1000 (0.125%)</td>
</tr>
</tbody>
</table>

*Stoll BJ et al. JAMA 2004

Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>cTn</th>
<th>cTn &gt; 3 W</th>
<th>Unadjusted p</th>
<th>Adjusted p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatory failure</td>
<td>25 (4-25)</td>
<td>25 (10-75)</td>
<td>0.28</td>
<td>0.015</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>21 (7-21)</td>
<td>13 (2-28)</td>
<td>0.05</td>
<td>0.1</td>
</tr>
<tr>
<td>Organ failure-free days</td>
<td>20 (5-20)</td>
<td>10 (1-20)</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>8.3 (4-16)</td>
<td>8.3 (4-16)</td>
<td>0.43</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*Adjusted for Pediatric Index of Mortality 3 score

Weiss SL et al Crit Care Med 2014

Association Between Antibiotic Use and Neonatal Mortality and Morbidities in Very Low-Birth-Weight Infants Without Culture-Proven Sepsis or Necrotizing Enterocolitis

Table 3. Regression analyses examining the neonatal outcomes in infants without infection-related morbidities

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary outcome</td>
<td>1.18 (1.13-1.23)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.04 (1.87-2.23)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.04 (1.00-1.10)</td>
</tr>
<tr>
<td>Persistent echocardiographic abnormality on neuroimaging</td>
<td>1.01 (0.96-1.05)</td>
</tr>
<tr>
<td>≥3 Stage retinopathy of prematurity</td>
<td>1.18 (1.06-1.32)</td>
</tr>
</tbody>
</table>

The inflammatory response

Various possible courses of the immune response to severe sepsis and septic shock

The developing human preterm neonatal immune system

In this article we use the term ‘biomarker’ in a very general sense to describe any measurable diagnostic indicator that is used to assess the risk or presence of disease.
Biological marker (biomarker): A characteristic that is **objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.**
Potential Biomarkers and their sensitivity in Neonatal Sepsis Infections

Ubiquitus Expression of the Calcitonin-I Gene in Multiple Tissues in response to Sepsis

Procalcitonin as marker and therapeutic target ins sepsis
Procalcitonin Increase after Endotoxin Injection in Normal Subjects

PARISH DANDONA, DAVID NIX, MICHAEL P. WILSON, AHMAD ALJADA, JOHN LOVE, MARCEL ASSICOT, AND CLAUDE BOHUON

Dandona P et J Clin Endocrinol Metab 1994

Procalcitonin is more likely to be released by the fetus rather than placental tissue during chorioamnionitis

Zbyněk Staněk, Jaroslav Feyerbrand, Peter Krczal, Simona Feyerbrandova, Ladislav Kofór

High serum procalcitonin concentrations in patients with sepsis and infection

Marcel Assicot, Dominique Griesel, Bruno Carron, Joëlle Raymond, Jean-Claude Clairmont

Fig 2—Serum procalcitonin concentrations in newborn infants (○) and older infants and children (●)

Procalcitonin as an early marker of infection in neonates and children

Van Rossum et al. Lancet Infectious Dis 2004
Postnatal age-specific percentile curve of serum PCT concentrations from birth to 12 weeks old in preterm infants


C-Reactive Protein, Interleukin-6, and Procalcitonin in the Immediate Postnatal Period: Influence of Illness Severity, Risk Status, Antenatal and Perinatal Complications, and Infection

ORIGINAL ARTICLE

Procalcitonin in preterm infants during the first few days of life: introducing an age related nomogram

D Turner, C Hammerman, B Rudovsky, Y Schleisiger, C Goaz, M S Schimmel
Procalcitonin as a Screening Test for Late-Onset Sepsis in Preterm Very Low Birth Weight Infants

Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPins)

Procalcitonin-guided decision making was superior to standard care in reducing antibiotic therapy in neonates with suspected early-onset sepsis.

Non-inferiority for re-infection or death could not be shown due to the low occurrence of re-infections and absence of study-related death.
IL-6 42251 pg/ml
CRP 139 mg/l
PCT 18.06 ng/ml

CRP 6 mg/L
PCT 1.57 ng/ml
IL-6 13488 pg/ml

Sepsis: a roadmap for future research

Lancet 2015
Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says Nicholas J. Schork.

Nature 2015

Metabolite Profiles in Sepsis: Developing Prognostic Tools Based on the Type of Infection

Sophie Neugebauer, MS(1); Evangelos I. Giannouli-Bourboulis, MD(2); Aminia Perlounou, MD(3); Andreas Mattoli, MD(3); Efstipanis Batoia, MD(3); Iuliu Tungarza, MD(3); Michael Bauer, MD(3); Michael Keshavjee, MD(3)

Summary and Conclusion

• The use of PCT should be considered within the context of the clinical workup and should take into account all patient-and therapy related factors that may interfere with the initial magnitude and the course of this parameter.
• Presently there is no single biomarker that fulfills all the criteria’s for becoming an ideal biomarker in neonatal sepsis
• Combination of several biomarkers may be more effective than single biomarkers, but this require further evaluation