Procalcitonin (PCT) Use in Sepsis Management and Antibiotic Treatment Decisions

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Overview of Sepsis

PCT utility in Sepsis management

PCT measurements and interpretation in clinical routine
Content

Overview of Sepsis

PCT utility in Sepsis management

PCT measurements and interpretation in clinical routine
What is sepsis

Sepsis is the body's overwhelming and life-threatening response to infection which can lead to tissue damage, organ failure, and death.

1. Graph: https://www.hli.ubc.ca/for-patients/the-sepsis-problem, accessed on 5-Jul-2016
Sepsis Etiology and Risk factors

1. Infants and seniors
2. People with chronic or serious illnesses, such as diabetes and cancer
3. Those who have an impaired immune system

Sepsis is a life-threatening and costly condition

- Leading cause of death in the US
- Estimated cases of sepsis among hospitalized patients each year in the U.S.
- People killed each year
- Recognition rate among U.S. adults, causing many patients to go untreated
- Increase in incidence of sepsis among hospitalized patients per year
- Annual costs to the U.S. healthcare system, most expensive to treat

Sepsis symptoms

S - Shivering, fever, or very cold
E - Extreme pain or general discomfort ("worst ever")
P - Pale or discolored skin
S - Sleepy, difficult to wake up, confused
I - "I feel like I might die"
S - Short of breath

Sepsis Stages: Defining a disease continuum
Based on 1992 and 2001 international consensus

**Stage**

**Sepsis**

(1992) Infection + ≥ 2 SIRS
- Temperature ≥38°C or ≤ 36°C
- HR ≥ 90 beats/min
- Respirations ≥ 20/min
- WBC count ≥ 12,000/mm³ or ≤4,000/mm³ or > 10% bands
- PaCO₂ < 32 mmHg

**Severe Sepsis**

Sepsis + Organ dysfunction
- Hypotension
- Hypoxia
- Elevated lactate
- Lab markers of end organ dysfunction

**Septic Shock**

Severe Sepsis + hypotension after adequate fluid resuscitation

**Disease manifestation**

**Mortality**

10-20%
20-50%
40-80%

Detecting sepsis early increases chances for survival!

Sepsis Stages: Defining a disease continuum

Based on 1992 and 2001 international consensus

**Stage**
- Sepsis
- Severe Sepsis
- Septic Shock

**Disease manifestation**

Sepsis (2001) Infection + possible signs of systemic inflammation

- General parameters
- Inflammatory parameters
- Hemodynamic parameters
- Tissue perfusion parameters

Sepsis + Organ dysfunction

- Hypotension
- Hypoxia
- Elevated lactate
- Lab markers of end organ dysfunction

Sepsis + hypotension after adequate fluid resuscitation

**Mortality**

- 10-20%
- 20-50%
- 40-80%

Detecting sepsis early increases chances for survival!

Sepsis Updated definition
Based on 2016 international consensus

Sepsis: life-threatening **organ dysfunction** caused by a dysregulated host response to **infection**.

* qSOFA: sepsis related organ failure assessment

Sepsis Management

Diagnostic Criteria
- Infection: Documented or suspected
- Inflammatory
- Organ dysfunction
- Hemodynamic
- Tissue perfusion

Treatment
- Initial resuscitation
- Antibiotic Therapy
- Source Control
- Fluid Therapy
- Vasopressors
- Corticosteroids
- Blood product Administration
- Glucose control
- Bicarbonate Therapy

Procalcitonin utility in Sepsis diagnosis and treatment described in the guideline.

Content

Overview of Sepsis

PCT utility in Sepsis management

PCT measurements and interpretation in clinical routine
What is procalcitonin (PCT)?

- Synthesized by the parafollicular C cells of the thyroid in a normal person
- Consists of 116 amino acids
- Peptide precursor of calcitonin, involved in calcium homeostasis
- LOW PCT values in the blood of healthy persons: 95% of subjects have values <0.1µg/L

Procalcitonin increases significantly as a systemic response to bacterial infection

The biomarker is

• Specific to bacterial infection
• Sensitive to systemic bacterial infection (difference in healthy vs. infected patients)
• Ubiquitously and uniformly expressed in multiple tissues throughout the body in response to systemic inflammation
• Lack of impact of anti-inflammatory and immunosuppressive states on production

Procalcitonin kinetics in bacterial infection

PCT has a rapid and sustained response to bacterially induced systemic inflammation

Daily measurement is recommended to properly follow PCT kinetics and assess disease onset and treatment effectiveness. Additional measurement may be done every 6-12 h.

PCT kinetics compared to other Inflammatory biomarkers

*PCT is a rapid marker that provides information about the course of the disease*

**Figure.** Kinetics of various markers of the inflammatory host response after endotoxin challenge in human volunteers. CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; TNF, tumor necrosis factor.

- **IL-6, IL-10, TNF:**
  - Quick onset but short half life, blood levels will not be detectable after 1-3 days. Not specific for bacterial infection.

- **PCT:**
  - Quick onset, half life 24 hour, correlate with disease severity reflect treatment effectiveness. Specific for bacterial infection.

- **CRP:**
  - Slower kinetic → slow to onset and slow to decrease after resolve of inflammatory course.

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Utility of procalcitonin in sepsis diagnosis and treatment

Key characteristics

✓ Sensitive
✓ Specific for bacterial infection
✓ Rapid rise/decline with control of infection
✓ Correlate with disease severity
✓ Not impaired by neutropenia or immunosuppressive states

Utilities

• Aid in diagnosis and risk stratification of bacterial sepsis
• Aid in elucidating prognosis of sepsis patients
• Predicating the need of antibiotic treatment in sepsis and to shorten duration of antibiotics required (reduce antibiotic exposure)
• To monitor therapeutic response to antimicrobial therapy
Procalcitonin demonstrated diagnostic values in suspected sepsis patients

Prospective study 1:

78 consecutive patients admitted with acute SIRS and suspected infection.

PCT, interleukin (IL)-6 and IL-8 were measured within 12h of admission. Biomarkers were compared in identifying critically ill patients with sepsis at admission.

<table>
<thead>
<tr>
<th></th>
<th>Procalcitonin</th>
<th>Interleukin-6</th>
<th>Interleukin-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff value, ng/ml*</td>
<td>1.1</td>
<td>200</td>
<td>30</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>97</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>78</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>94</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>88</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Area under the receiver operating curve (95% confidence interval)</td>
<td>(0.85–1.0)</td>
<td>(0.63–0.87)</td>
<td>(0.59–0.83)</td>
</tr>
</tbody>
</table>

Figure: ROC of plasma parameters (PCT; IL-6; and IL-8; upper panel), and of a clinical model with and without PCT (lower panel). Areas under the ROC were: upper panel, PCT, 0.92; IL-6, 0.75; IL-8, 0.71; and lower panel, clinical model with PCT, 0.94, and clinical model without PCT, 0.77.

Procalcitonin demonstrated performance superior to that of other biomarkers for sepsis Diagnosis

Prospective study 2:
101 consecutive critically ill patients presented to ICU in a university medical center who are diagnosed with SIRS, sepsis, severe sepsis or septic shock.

PCT, CRP, IL-6, IL-8, and lactate were measured on day 1, day 2 and the day of discharge from ICU or death. measurements in identifying critically ill patients with sepsis

Table 3. Evaluation of laboratory parameters for the diagnosis of sepsis in a medical intensive care unit (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin precursors (1 ng/mL)</td>
<td>89</td>
<td>94</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>Interleukin-6 (50 pg/mL)</td>
<td>65</td>
<td>79</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>C-reactive protein (100 mg/L)</td>
<td>71</td>
<td>78</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Lactate (2 mmol/L)</td>
<td>40</td>
<td>77</td>
<td>58</td>
<td>61</td>
</tr>
</tbody>
</table>

Numbers in parenthesis denote cutoff values.

Figure: ROC of plasma parameters (PCT; CRP, IL-6 and lactate. Values are shown for all time points (n=272; 101 values at admission;, 74 values on day 2 and 97 values on day of discharge or death). Areas under the curve indicate that procalcitonin is the most reliable marker for the diagnosis of sepsis (p=0.01).
Prospective study 2:
101 consecutive critically ill patients presented to ICU in a university medical center who are diagnosed with SIRS, sepsis, severe sepsis or septic shock.
PCT, CRP, IL-6, IL-8, and lactate were measured on day 1, day 2 and the day of discharge from ICU or death. Measurements in identifying critically ill patients with sepsis

Prospective study 3:
40 surgery intensive care patients from a tertiary health care institution with SIRS or sepsis are included.
PCT and CRP plasma levels, SOFA scores were determined daily 1-5 days and 8-15 days after onset.

Procalcitonin is an independent predictor of mortality risk in septic patients

Prospective study 4:
144 patients presenting severe sepsis or septic shock to IMC. PCT was measured within the first hour after admission and day 1 and day 3. Kinetics of PCT is defined by variation between admission to 72 hours and 24-72 hours. 30 day mortality risk was evaluated in ΔPCT decrease < 15% or <20%

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Δ-PCT % variation</td>
<td></td>
</tr>
<tr>
<td>Δ-0-72h decrease &lt; 15%</td>
<td>6.1</td>
</tr>
<tr>
<td>Δ-24-72h decrease &lt; 20%</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Prospective study 5:
598 patients presenting severe sepsis or septic shock admitted to ICU. PCT was measured daily for the first 5 days. Kinetics of PCT is defined by variation between admission or next day to day 4. 28 day mortality risk was evaluated in ΔPCT decrease >80% or ≤ 80%.

24. Elecsy Brahms PCT package Insert
Procalcitonin guided antibiotic therapy showed decreased antibiotics use with no significant effect on patient outcomes

Use of PCT-guided antimicrobial therapies demonstrated benefits of patient outcomes:

- 21-38% relative reduction in the duration of antibiotics therapy
- PCT guided Abx discontinuation showed reduced antibiotic duration by 2.05 days (95% CI: -2.59 to -1.52) in ICU patients
- No significant difference amongst mechanical ventilator-free days, infection recurrence or mortality.
- One study of neonates with suspected sepsis demonstrated reduced antibiotic duration by 22.4 hours and reduced the proportion of neonates on antibiotics for ≥72 hours by 27%

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Procalcitonin guidance to reduce duration of antibiotic treatment in critically ill patients is effective and safe

Prospective study 6:

Multicenter randomized controlled open label interventional trial. Critically ill with assumed or proven infection receiving antibiotics were randomly assigned (N = 538, PCT guided; N = 457, control group). PCT is measured daily, including baseline measurement as close to initiation of antibiotics. Non-binding advice to discontinue antibiotics when PCT concentration decrease by > 80% or ≤0.5ug/L. Standard care group receive local antibiotic protocol.

<table>
<thead>
<tr>
<th></th>
<th>Procalcitonin-guided group (n=761)</th>
<th>Standard-of-care group (n=785)</th>
<th>Between-group absolute difference in means (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic consumption (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily defined doses in first 28 days</td>
<td>7.5 (4.0 to 12.8)</td>
<td>9.3 (5.0 to 16.5)</td>
<td>2.69 (1.26 to 4.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>5.0 (3.0 to 9.0)</td>
<td>7.0 (4.0 to 11.0)</td>
<td>1.22 (0.65 to 1.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antibiotic-free days in first 28 days</td>
<td>7.0 (0.0 to 14.5)</td>
<td>5.0 (0.0 to 13.0)</td>
<td>1.31 (0.52 to 2.09)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>149 (19.6%)</td>
<td>196 (25.0%)</td>
<td>5.4% (1.2 to 9.5)</td>
<td>0.0122</td>
</tr>
<tr>
<td>1-year mortality</td>
<td>265 (34.8%)</td>
<td>321 (40.9%)</td>
<td>6.1% (1.2 to 10.9)</td>
<td>0.0158</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinflection</td>
<td>38 (5.0)</td>
<td>23 (2.9)</td>
<td>-2.1% (4.1 to -0.1)</td>
<td>0.0492</td>
</tr>
<tr>
<td>Repeated course of antibiotics</td>
<td>175 (23.0)</td>
<td>173 (22.0)</td>
<td>-1.0% (5.1 to 3.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Time (days) between stop and reinstition of antibiotics</td>
<td>4.0 (2.0 to 8.0)</td>
<td>4.0 (2.0 to 8.0)</td>
<td>-0.22 (-1.31 to 0.88)</td>
<td>0.96</td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cumulative costs of antibiotics</td>
<td>€150,082</td>
<td>€181,263</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median cumulative costs antibiotics per patient</td>
<td>€107 (51 to 229)</td>
<td>€129 (66 to 273)</td>
<td>€33.6 (2.5 to 64.8)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On the intensive care unit</td>
<td>8.5 (5.0 to 17.0)</td>
<td>9.0 (4.0 to 17.0)</td>
<td>-0.21 (-0.92 to 1.60)</td>
<td>0.56</td>
</tr>
<tr>
<td>In hospital</td>
<td>22.0 (13.0 to 39.3)</td>
<td>22.0 (12.0 to 40.0)</td>
<td>0.39 (-2.69 to 3.46)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA = not applicable.

Table 2: Primary and secondary outcome measures

Summary of clinical evidence

- **Diagnosis**
- **Risk assessment**
- **Prognosis**

**PCT measurement**

- **Day 0**
- **Day 1**
- **Day 2**
- **Day 3**
- **Day 4**
- **Day 5**
- **Day 6**
- **Day 7**

Guide antibiotic Initiation / discontinuation
Monitor treatment effectiveness
Risk assessment
## Limitations of procalcitonin

<table>
<thead>
<tr>
<th>Falsely high</th>
<th>Falsely low</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Newborns (&lt;48-72 hours; after 72 interpret levels as usual)</td>
<td>• very early presentation of systemic infection</td>
</tr>
<tr>
<td>• Massive stress (severe trauma, surgery, cardiac shock, burns)</td>
<td>• localized infection such as an abscess</td>
</tr>
<tr>
<td>• Treatment with agents which stimulate cytokines</td>
<td></td>
</tr>
<tr>
<td>• Malaria and some fungal infections</td>
<td></td>
</tr>
<tr>
<td>• Prolonged, severe cardiogenic shock or organ perfusion abnormalities</td>
<td></td>
</tr>
<tr>
<td>• Some forms of vasculitis and acute graft vs. host disease</td>
<td></td>
</tr>
<tr>
<td>• Significantly compromised renal function</td>
<td></td>
</tr>
</tbody>
</table>

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# Comparison of clinical biomarkers used in Sepsis

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Specific for infection</th>
<th>Sensitive to inflammation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+</td>
<td>++++</td>
<td>Simple, sensitive</td>
<td>Non-specific</td>
</tr>
<tr>
<td>WBC</td>
<td>+</td>
<td>+++</td>
<td>Simple, sensitive</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Cytokines</td>
<td>+</td>
<td>+++</td>
<td>Sensitive Rapid onset (1-3h) Also increase in local effusions</td>
<td>highly variable short half life Expensive</td>
</tr>
<tr>
<td>C-reactive Protein (CRP)</td>
<td>++</td>
<td>++</td>
<td>Inexpensive, moderate specific to sepsis</td>
<td>Slow onset and reduction (peak &gt; 24h) No correlation with severity</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>++++</td>
<td>+</td>
<td>Specific Rapid onset (6-12h) Correlate with disease severity and reflect treatment effectiveness</td>
<td>Low sensitivity for localized infection Need education</td>
</tr>
<tr>
<td>Lactate</td>
<td>+</td>
<td>+</td>
<td>Marker of impaired oxidative metabolism and perfusion abnormalities</td>
<td>Not early indicator of sepsis lacks specificity</td>
</tr>
</tbody>
</table>


## Comparison of procalcitonin and blood culture utility in sepsis

<table>
<thead>
<tr>
<th></th>
<th>Blood Culture</th>
<th>Procalcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used to detect:</td>
<td>Existence and type of pathogens in the blood</td>
<td>Systemic host response to bacterial infection</td>
</tr>
<tr>
<td>Results after suspicion of sepsis</td>
<td>6 hours to 2~3 days</td>
<td>Rapid increase, results can be obtained in ~ 20 min (+ logistics)</td>
</tr>
<tr>
<td>Sensitivity/specificity</td>
<td>Observed high contamination and false negative rate</td>
<td>High sensitivity and specificity, some limitation of false high/low results</td>
</tr>
<tr>
<td>Use in ABx treatment</td>
<td>Pathogen specific Abx treatment</td>
<td>Initiate and de-escalate treatment, monitor treatment effectiveness</td>
</tr>
</tbody>
</table>

Content

Overview of Sepsis

PCT utility in Sepsis management

PCT measurements and interpretation in clinical routine
Recommendation for incorporating PCT in practice

Evaluate the following two variables:

✓ The availability of PCT assays in-house is necessary for the biomarker to be used in an efficient and cost-effective manner.

✓ While using PCT to assist in developing a specific plan, it is important to remember to include the biomarker into the overall clinical assessment.

Example 1:
Use Procalcitonin to assess 28-day risks of all-cause mortality in patients diagnosed with severe sepsis or septic shock

\[
\Delta PCT = \frac{PCT_{\text{Day0 (or Day1)}} - PCT_{\text{Day4}}}{PCT_{\text{Day0 (or Day1)}}} \times 100\%
\]

1. **Patient diagnosed with “severe sepsis” or “septic shock”**
2. **\( \Delta PCT \) (%): Change of PCT levels over the first 4 days**
3. **\( \Delta PCT > 80\% \)**
   - Test negative: Lower mortality risk
4. **\( \Delta PCT \leq 80\% \)**
   - Test positive: Higher mortality risk
Application:
Procalcitonin: assessing 28-day risks of all-cause mortality in patients diagnosed with severe sepsis or septic shock

\[ \Delta \text{PCT} = \frac{(30-4)}{30} \times 100\% = 86.7\% \]
Together with clinical course, indicate lower 28-day all-cause mortality risk

\[ \Delta \text{PCT} = \frac{(30-20)}{30} \times 100\% = 33.3\% \]
Together with clinical course, indicate higher 28-day all-cause mortality risk
Example 2: Use PCT levels to assess risks for sepsis and severe sepsis and septic shock

**Normal**: <0.1 ng/mL (infants >72 hours – adults)

**Suspected Sepsis**: Strongly consider initiating antibiotics in all unstable patients.

0.1 – 0.5 ng/mL - Low likelihood for sepsis;

>0.5 ng/mL – Increased likelihood sepsis;

>2.0 ng/mL – High risk of progression to severe sepsis/septic shock

Example 3: Use procalcitonin to initiate antibiotic use in Sepsis patients

![Sepsis Initial Antibiotic Use Algorithm](image)

PCT Value

- <0.25 µg/L
- 0.25 - 0.49 µg/L
- ≥0.5 - 1.0 µg/L
- >1.0 µg/L

Antibiotic Use Recommendation

- Strongly Discouraged
- Discouraged
- Encouraged
- Strongly Encouraged

- Consider alternative diagnosis
- Repeat PCT in 6-12 hours if antibiotics not begun
- If clinically unstable, immunosuppressed or high risk consider overruling

Repeat daily for 3 days to consider early antibiotic discontinuation

See Algorithm 4

Example 4: Use procalcitonin in de-escalation of antibiotic use

![Sepsis Follow PCT Antibiotic Use Algorithm](image)

Application:
Interpreting PCT trend after the critically ill patient admitted with suspected sepsis and is given antibiotics

Daily PCT levels showed consistent downward trend, indicating immediate effectiveness of Abx. Consider discontinue of Abx from Day 6.

Daily PCT level showed upward trend, showing no response to Abx. Evaluate cause of upward trend (therapy failure) and consider different Abx treatment, source control, etc. is necessary.

Application:
Interpreting PCT trend after the critically ill patient admitted with suspected sepsis and is given antibiotics

Daily PCT levels showed consistent low results below 0.5 ng/mL, indicating no systemic response to bacterial infection. Consider looking for different diagnosis, stop antibiotics, or reasons for falsely low PCT.

Daily PCT levels showed secondary response to therapy after change of antibiotics at day 4.

Key Principles of PCT interpretation

Clinical Context

Serial measurements

Disease Dynamics

PCT

Limitations

Summary

1. Sepsis is a condition of host dysregulated response to infection. Early detection and management is critical.

2. Procalcitonin showed promising clinical utilities in sepsis diagnosis, risk assessment and antibiotic treatment decisions.

3. Interpretation of procalcitonin trends during the patient management should be considered together with clinical contexts and dynamics of the disease.
References

1. Graph: https://www.hli.ubc.ca/for-patients/the-sepsis-problem, accessed on 5-Jul-2016
References

24. Elecys Brahms PCT package Insert

Doing now what patients need next