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Procalcitonin (PCT)

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Introduction

- Sepsis is the systemic response to infection by microbial organism which is caused by either bacteria or other microbial organism which is essential for effective treatment and prognostic assessment.

- Current clinical laboratory methods in the diagnosis of bacterial infection are either non-specific or require longer times.

- A number of the inflammatory markers such as leukocyte cell count, C reactive Protein (CRP), and cytokines (TNF-α, IL-1β, or IL-6), have been applied in the diagnosis of inflammation and infection, but their lack of specificity has generated a continued interest to develop more specific clinical laboratory tests.
Definition

Procalcitonin (PCT): is a 116 amino acid peptide that has approximately MW 14.5 KDa and it belong to calcitonin (CT) which is hormone secreted from Para-follicular C cell of the thyroid gland.

Procalcitonin (PCT) also produced by the neuroendocrine cell of the lung and intestine and is released as an acute phase reactant in response to inflammatory stimuli, especially those of bacterial origin.

The physiological importance of Procalcitonin is not well understood, but some hypotheses suggest that it may involve in metabolism of calcium, cytokines network and modulation nitric oxide (NO) synthesis, as well as pain-relieving effect.
No enzyme in the plasma break down it. therefore, once it enters the circulation, it remains unchanged, with a half life around 30 hours, with no evidence that it binds to cellular receptor of calcitonin or any specific Procalcitonin receptor.

Procalcitonin (PCT) act as a biomarker that exhibit greater specificity than other pro-inflammatory markers (e.g. cytokines) in identifying patient with sepsis and can be used in the diagnosis of bacterial infection.

Normal range: <0.1 ng/mL (infants >72 hours – adults).
Abbreviations used:
PCT, procalcitonin; CT, calcitonin; CCP-1, calcitonin carboxypeptide-1; PAM, peptidylglycine α-amidating monooxygenase.
PROCALCITONIN – NORMALLY AN INTERMEDIATE PRODUCT IN THE SYNTHESIS OF CALCITONIN

After P. Linscheid, Endocrinology 2003

LOW PCT values in the blood of healthy persons: 46.7 pg/ml (97.5 percentile); median = 12.7 pg/ml*
Calcitonin: Sources of production in healthy people

<table>
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<tr>
<th>Tissue</th>
<th>Healthy</th>
<th>Sepsis</th>
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<td>Thyroid</td>
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<td>White Blood Cells</td>
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<td>Perit. Macrophage</td>
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<td>Visceral Fat</td>
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<td>Testes</td>
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PCT: Sources of Production in Septic Patients

- In bacterial infection, PCT is produced and released into circulation from the entire body.
Sepsis

- Sepsis refer to systemic response to infection by microbial agents, such as bacteria, fungi, yeast, the patient typically develops fever, tachycardia, tachypnea, and leukocytosis. Its also associated with hypo-perfusion or dysfunction of at least 1 organ.

- When its accompanied by hypotension or multiple organ system failure it call septic shock.

- The signs & symptoms of sepsis are variable and are influencing by many factors like virulence and bio-burden of the pathogens, the portal entry and the host susceptibility.
Primary sits are Respiratory tract infection, then genitourinary, then gastrointestinal infections.

Recently there has been increasing numbers of bacterial infections in hospitalized patients due to increased nosocomial infection from catheterization and immunosuppressive drugs also increased causes of (MRSA).

A common problem in the clinical practice is that the sign and symptoms of bacterial and viral infections are widely overlapping especially in Respiratory tract infection.

The diagnostic uncertainty still remains, even after obtaining a patient history, performing a physical examination, chest x-ray and laboratory tests.
So a laboratory test with more specificity would significantly improve the clinical differential diagnosis in these cases.

Also the differential diagnosis of infection would help in deciding whether treatment with antibiotics would be beneficial.

So, the excessive use of antibiotics is the main cause for the spread of antibiotics-resistance bacteria. Thus, decreasing its usage is essential in combating the increase of antibiotics-resistance microorganism.
PRESENCE OF BACTERIAL INFECTION STIMULATES PCT PRODUCTION

Alternative synthesis of PCT

- Bacterial toxins (gram+/-) and cytokines **stimulate production** of PCT in all parenchymal tissues
- PCT is **immediately released** into bloodstream
- This process can be **blocked** during viral infections
- IFN-γ released in viral infection, **blocks** the activation of PCT production, therefore in viral infection PCT levels remain normally low
- In critically ill patients, **PCT levels elevate in correlation to the severity of bacterial infection**.
- In healthy people, PCT concentration are found **below 0.05ng/ml**.
- **Concentrations exceeding 0.5ng/ml** can be interpreted as abnormal.
Diagnostic methods for sepsis

- Culture (blood, urine, CSF, bronchial fluid).
- Clinical symptoms frequently manifest themselves in the absence of positive culture.
- Routine laboratory tests for sepsis such as CPR, leukocyte count, lack diagnostic accuracy and sometimes misleading.
- In severe infections, most classical pro-inflammatory cytokines such as TNF-α, IL-1β, or IL-6, are increased only briefly or intermittently.
- So, a more unequivocal test for the differential diagnosis of infection and sepsis is very important.
Indications

- Indications for serum PCT measurements include the following:
  - To aid in the diagnosis and risk of bacterial sepsis.
  - To aid in the diagnosis of renal impairment in children with UTI.
  - To aid in distinguishing bacterial from viral infections, including meningitis.
  - To monitor therapeutic response to antibacterial therapy and reduce antibiotics exposure.
  - To aid diagnosis of systemic secondary infection after surgery and in severe trauma, burns, multi-organ failure.
  - To aid diagnosis of infected necrosis and associated systemic complication in acute pancreatitis.
Proposed application of serum PCT measurement include the following:

- To aid the choice and timing of the initiation of antibiotics treatment.
- To aid with explanting prognosis of critically ill patient with systemic infection.
- To assist with explanting prognosis of severe localized infections (e.g. Pneumonia).
- Predicting the need of antibiotics treatment in sepsis and to shorten the duration of antibiotics required.
- Use as independent predictor of graft failure after renal transplantation.
PCT in the diagnosis of bacterial infection

- In 1990s, there has been increasing use of PCT measurement in identifying systemic bacteria infections.

- It has an a short half life (25-30 hours in plasma).

- Some studies have shown that:
  1. An increase in PCT level is minimal in viral infection while level rapidly increase after a single injection with endotoxin.
  2. Its not associated with specific bacterial strains.
  3. It could help rule out nosocomial infection in newborn hospitalized in ICU.
  4. PCT level in blood of patient infected with (CAP) caused by Legionella pneumonaphila in comparision to (CRP,WBCs) was initial high levels more with sever dis. & in patient has a longer stay in ICU.
  5. Persistant high levels of PCT were indicate a unfavorable outcome.
General PCT interpretation

- **Sepsis:**
  - >2.0 µg/L predicts sepsis.
  - >10 µg/L indicate likely septic shock.
  - Sensitivity and specificity of PCT for the diagnosis of sepsis has varied based upon population and underlying diseases, Higher PCT levels have been shown to be associated with a worse prognosis.

- **Febrile Children:**
  - >2.0 µg/L make a serious infection much more likely.
  - <0.5 µg/L make a serious infection much less likely.
  - 0.5 and 2.0 µg/L are equivocal and generally not helpful. Consider repeating in 6-12 hours verses initiating therapy depending on clinical judgment.
Cont.

- Bacterial Meningitis:
  - Most patients with bacterial meningitis have much higher PCT levels (>5 µg/L).

- Renal Involvement In Children With UTI:
  - PCT values of >0.5 µg/L have a sensitivity of 70-90% and 80-90% specificity for renal involvement in pediatric patients with UTIs.
<table>
<thead>
<tr>
<th>PCT (ng/mL)</th>
<th>Possible causes</th>
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<tbody>
<tr>
<td>&lt;0.05</td>
<td>Normal values</td>
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<tr>
<td></td>
<td>Local inflammation or infection is possible, systemic inflammatory response unlikely</td>
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<td>On first day of ICU admission indicates a low risk for progression to severe sepsis and/or septic shock</td>
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<tr>
<td>≥0.5 and &lt;2.0</td>
<td>Systemic inflammatory response present due to infection, or severe trauma, or major surgery or cardiogenic shock</td>
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<tr>
<td></td>
<td>If the patient has a proven infection it could be sepsis</td>
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<tr>
<td>≥2.0 and &lt;10</td>
<td>Likely to be sepsis (severe systemic inflammatory response due to infection)</td>
</tr>
<tr>
<td></td>
<td>On first day of ICU admission indicates a high risk for progression to severe sepsis and/or septic shock</td>
</tr>
<tr>
<td>≥10</td>
<td>Severe sepsis or septic shock</td>
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<td></td>
<td>Organ dysfunction</td>
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<td>High risk of death</td>
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PCT measurements in other diseases

- **Malaria**: it elevated in both severe and uncomplicated *Plasmodium Falciparum* malaria, but it couldn’t differentiate between its types.

- **Pulmonary TB (PTB)**: serum PCT levels were slightly high on admission of patient with active PTB in comparison with the controlled and patient on anti-TB drugs.

- **Pneumonia**: PCT level could be useful in distinguishing (CAP) due to bacteria such as *Mycobacterium tuberculosis* (TB) and *Pneumocystis jirovecii* (PJP) in a high HIV prevalence.
Cont.

Transplantation: PCT level was useful in identifying whether inflammation following an organ transplant is due bacterial infection or organ rejection, it can also determine the prognosis and postoperative complication in transplant patient.

Transplantation: PCT level elevated in transplant patient who receiving pan T-cell antibody, both with CRP elevated in patient scheduled for hematopoietic stem cell transplantation receiving anti-thymocyte globulin.

Adrenal failure: PCT level elevated in Addisonian crisis in adrenal failure.

Massive stress: PCT level elevated in severe trauma, surgery, cardiac shock, burns.
Drugs: PCT level elevated with using agent which stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, granulocyte transfusion).

Malignancy: PCT level elevated in Para-neoplastic syndromes due to medullary thyroid and small cell lung cancer (may exceed 10,000 ng/mL).

Kidney Disease: it increased in significantly compromised renal function, especially ESRD/hemodialysis.

Circulatory failure: PCT level also raised in prolonged, severe cardiogenic shock or organ perfusion abnormalities.
Low PCT Level

- Low PCT level in the presence of bacterial infections may occur in:
  - Early course of infection: re-measure in 6-12 hrs.
  - Sub-acute endocarditis.
  - Localized infections.
  - Self-limiting bacterial infection.
SERIAL MEASUREMENT OF PCT PROVIDES A CLEARER PICTURE OF THE PATIENT’S RESPONSE TO ANTIBIOTIC TREATMENT.

- **Decreasing PCT levels** in patients with sepsis indicate effective treatment of the underlying infection.

- **Persistently elevated PCT levels** indicate a possible treatment failure.
PCT guidance significantly shortens the time that patients need to be on antibiotics (reduces AB exposure and their adverse effects).

**Key takeaway:**
Tailoring of AB treatment using PCT to the individual patient needs safely led to a reduction of average treatment duration from **12 to 5 days** with same outcome.
PCT in Newborn (<72 hours)

- Reference values have not been established in infants younger than 72 hours.

- In neonates aged less than 72 hours, a procalcitonin level of more than 1 ng/mL at birth, 100 ng/mL or more at age 24 hours, and 50 ng/mL or more at age 48 hours suggests serious bacterial infection.

- In children with urinary tract infection, a procalcitonin level of more than 0.5 ng/mL suggests renal involvement.
Procalcitonin VS. C-reactive protein

- CRP is the most common laboratory marker used in the clinical setting to evaluate systemic inflammatory response to an infectious agent. It is routinely used as a diagnostic, predictor, and monitoring marker in patients with acute sepsis.

- Several recent comparison studies have aimed to determine the use of PCT in conjunction with CRP or independent of it in the setting of severe bacterial infections.

- PCT is a more useful diagnostic inflammation parameter than CRP in patients with pediatric neutropenic fever, both in estimating the severity of infection and the duration and origin of the fever.

- PCT is a useful early diagnostic marker for detection of bacteremia in febrile neutropenia and has better diagnostic value than CRP.
PCT kinetics provide important information on prognosis of sepsis patients

- Clinical symptoms alone are often insufficient for early and accurate diagnosis
- PCT levels, can be observed within 3-6 hours after an infectious challenge with a peak - up to 1000 ng/ml - after 6-12 hrs. Half-life: ~24hrs
- Specific to bacterial origin of infection and reflects the severity of the infection
DIAGNOSTIC ACCURACY OF PCT COMPARED TO OTHER BIOMARKERS USED IN SEPSIS

- PCT levels accurately differentiate sepsis from noninfectious inflammation*
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

*Sensitivity: 89%
Specificty: 94%
NPV: 90% / PPV: 94%
Thank You