PROCALCITONIN AS AN EARLY BIOMARKER FOR DIFFERENTIATION BETWEEN ACUTE BACTERIAL AND VIRAL UPPER RESPIRATORY TRACT INFECTION IN CHILDREN


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DIFFERENTIATION BETWEEN ACUTE BACTERIAL
AND VIRAL UPPER RESPIRATORY
TRACT INFECTION IN CHILDREN

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ABSTRACT

The level of procalcitonin (PCT) in children is undetectable in healthy individuals and slightly increased in viral infections and noninfectious inflammatory responses. It has been described to be notably increased in bacterial, parasitic, or fungal infections.

Acute respiratory tract infections (ARTI) of this study include, pharyngitis, tonsillitis, rhinosinusitis, otitis media. As much as 75% of antibiotics are prescribed for ARTI, despite the mainly viral origin.

The objective of this trial is to evaluate, if a PCT-guided diagnostic strategy leads to reduction of antibiotic use for patients with ARTI in primary care compared to standard approaches as C-reactive protein (CRP) and total leucocytic count (TLC).

This study included 110 children, 20 of them were apparently healthy as a control group. The diseased group; 30 children with pharyngotonsillitis, 30 children had acute rhinosinusitis and 30 children with acute otitis media.

PCT, CRP and TLC were evaluated for control and diseased groups. Culture for diseased group from blood, post nasal and ear discharge was done. Also, detection for adenovirus and respiratory syncetial virus antigen
had been performed.

No significant difference was observed between 2 groups as regards age and sex distribution. In the diseased group; 43 (47.8%) children had viral infection and 52.2% had bacterial ARTI.

Procalcitinin level was significantly higher in children with bacterial infection (6.9 ± 1.63 ng/L) than those with viral ARTI (0.9 ± 2.8 ng/L) and non-infected or control group (0.1 ± 0.4). The mean value for CRP was 5.1 ± 1.8, 32 ± 13.8 and 12 ± 7.1 in control, bacterial and viral groups.

The mean value of TLC was 10.1 ± 5.8, 19.1 ± 6.9 and 12.1 ± 7.3 for the groups respectively with no significant value.

It was concluded that the procalcition level had higher sensitivity, specificity for differentiation bacterial and viral infections than C reactive protein or leucocytic count. So PCT may be a guide for using antibiotic therapy by differentiating bacterial from viral ARTI.

**Introduction**

Procalcitonin (PCT), a protein of 116 amino-acids was discovered as a prohormone of calcitonin produced by C-cells of the thyroid gland and intracellularly cleaved by proteolytic enzymes into the active hormone. Circulating levels of PCT in healthy subjects are below detection limit. Blood concentrations of procalcitonin are increased in systemic inflammation, especially when this is caused by bacterial infection. Studies of its behavior in patients with bacterial sepsis have led to the proposal that it may be useful marker of systemic bacterial infection, with greater specificity and sensitivity than acute phase proteins such as C-reactive protein(1).

Both C-reactive protein (CRP) and procalcitonin (PCT) are accepted sepsis markers. However, there is still some debate concerning the correlation between their serum concentrations and sepsis severity, but it's plasma level markedly increases, mostly due to extra-thyroidal production in cases of severe infections (bacterial, parasitic and fungal) with systemic manifestations, especially in the presence of septic shock. Since noninfectious inflammatory reaction, viral infection
and localized bacterial infections manifest only small to modest increases of procalcitonin in plasma, procalcitonin levels may be useful in differentiating between these diseases and sepsis. In addition, it has been suggested that procalcitonin is an early and good marker of elevated cytokines in patients with sepsis, and that its plasma level is correlated with Sepsis. Since plasma procalcitonin is measured easily, quickly and accurately by immunoluminometric assay, it is useful for early diagnosis of sepsis in patients with severe systemic inflammatory response syndrome and as an indicator of severity of sepsis in such patients(2).

PCT remains constantly low in patients infected with viruses or suffering from inflammatory diseases. Unlike other markers such as ESR and CRP, PCT remains low during episodes of known inflammatory diseases such as Lupus, connective tissue disease, inflammatory rheumatism(3).

ARTI are the most frequent reasons for consultations in primary care. Although predominantly viral in origin, ARTI often lead to the prescription of antibiotics for ambulatory patients, mainly because it is difficult to distinguish between viral and bacterial infections.

Several studies indicate that the main reasons for antibiotic prescription in ambulatory patients with ARTI are non-medical and related to the physician-patient relationship, patient’s expectations and beliefs about the benefit of antibiotics. Thus, in theory a reduction of antibiotic prescriptions and duration can also be achieved by the implementation of guidelines. However, in practice physician education and guidelines dissemination for ARTI management usually show no clinically relevant effect(4),(5),(6).

The aim of our work is to study the markers of infections procalcitonin, CRP and total leucocytic count in bacterial and viral ARTI to stop the unnecessary antibiotic use.

Subjects and Methods:

This study was carried out on 90 children with acute respiratory tract infection, with ages ranging from 2-16 years in addition to 20 children with age matched, apparently healthy normal subjects as a control group. Patients were selected from ENT department of Benha University Hospital and Said Galal hospital during the period from Sept. 2004 to Feb. 2005.

Subjects included in the study were classified into following groups:

Group I : Control group (20 patients).

Group II : Patient group (90 patients).
This group subdivided after complete ENT examination into the following three subgroups:
- Acute pharyngotonsillitis group (30 patients)
- Acute rhinosinusitis group (30 patients)
- Acute otitis media group (30 patients).

All children in all groups had not receive antibiotics for 7 days before the study, and consent of parent was taken.

Methodology:
- **One ml blood on EDTA:**
  For total leucocytic count using Sysmex KX 21 To A medical electronics, Roche Diagnostics GmH, KD 68298 Manheim, Germany, Roche Diagnostic corporation, Indianapolis, 11N, USA and stained film by leishman stain for differential count.
- **Serum samples for measuring:**
  - CRP by laser nephelometric technique using Dade Behring BN Prospe-Dade Behring Marburg GmbH-str. 76-D-35041 Marburg/ Germany, expressed as mg/dl.
  - Serum PCT concentrations were determined by means of a specific and ultrasensitive immunoluminometric assay (LUMI test) measured on kryptor fully automated immunoassay system (Brahms, Hennigsdorf/ Berlin, Germany) expressed as ng/ml.

- **Blood culture by using oxoid media was done.**
- **Culture on blood agar and maeconkey media:** for post nasal disarage and ear swabes.
- **Nasal wash and nasal aspirate specimens:** wash and aspirate were done for direct antigen detection for respiratory syncetial virus (RSV) and adeno virus by using Pathfinder™ (ELIZA technique) from Bio-Rad-Laboratories)
*Procalcitonin as an Early Biomarker for Differentiation*

For statistical analysis SPSS for windows was used to calculate mean ±SD, correlation, paired t and unpaired t test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

**RESULTS:**

Data was ordered, processed and tabulated in as following:

**Table (1): Clinical data of the studied groups:**

<table>
<thead>
<tr>
<th>Studied groups (N)</th>
<th>Range of age (Mean ±SD)</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (20)</td>
<td>2-16 (5.6 ±4.1)</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Acute pharyngotonsillitis (30)</td>
<td>2-15 (6.4 ± 3.2)</td>
<td>17</td>
<td>13</td>
<td>70.50</td>
</tr>
<tr>
<td>Acute rhino sinusitis (30)</td>
<td>2.5 - 16 (6.1 ± 3.9)</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Acute otitis media (30)</td>
<td>2-14 (5.1 ± 43)</td>
<td>16</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

No significant correlation was detected between age and sex in the different studied groups.

**Table (2): Bacterial and viral infection in diseased group:**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Viral N (%)</th>
<th>Bacterial N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute tonsillitis (30)</td>
<td>16 (53.4%)</td>
<td>14 (53.4%)</td>
</tr>
<tr>
<td>Acute rhinosinusitis(30)</td>
<td>14 (46.6%)</td>
<td>16 (53.4%)</td>
</tr>
<tr>
<td>Acute otitis media (30)</td>
<td>14 (46.8%)</td>
<td>17 (56.7%)</td>
</tr>
<tr>
<td>Total (90)</td>
<td>43 (47.8%)</td>
<td>47 (52.2%)</td>
</tr>
</tbody>
</table>

Forty three out of 90 children with ARTI had viral infection.
Table (3): The mean of CRP & TLC and PCT in bacterial and viral infection

<table>
<thead>
<tr>
<th>Groups</th>
<th>CRP mg/dl</th>
<th>TLC (10³/CC)</th>
<th>PCT (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.1 ± 1.8</td>
<td>10.1 ± 5.8</td>
<td>0.1 ± 0.4</td>
</tr>
<tr>
<td>Bacterial</td>
<td>32 ± 13.8</td>
<td>19.1 ± 6.8</td>
<td>6.9 ± 16.3</td>
</tr>
<tr>
<td>Viral</td>
<td>12 ± 7.1</td>
<td>12.1 ± 7.3</td>
<td>0.9 ± 2.8</td>
</tr>
</tbody>
</table>

Table (4): Positive culture in the diseased group:

<table>
<thead>
<tr>
<th>Culture (type of sample)</th>
<th>Pharyngotonsillitis 30 child</th>
<th>Acute rhinosinusitis 30 child</th>
<th>Acute otitis media 30 children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Post nasal swab</td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Ear swab</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

N.B.: The same case may have more than one +ve culture.

Table (5): Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for PCT, CRP and TLC.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>98.4</td>
<td>95.9</td>
<td>96.1</td>
<td>98.8</td>
</tr>
<tr>
<td>WBCs</td>
<td>94.2</td>
<td>65.9</td>
<td>46.1</td>
<td>93.9</td>
</tr>
<tr>
<td>CRP</td>
<td>96.1</td>
<td>85.9</td>
<td>70.9</td>
<td>94.9</td>
</tr>
</tbody>
</table>

PCT is the highest in specificity, sensitivity, PPV and NPV.
DISCUSSION

Criteria often used in clinical practice to distinguish bacterial from viral infections of the respiratory tract include fever, dyspnea, purulent sputum, chest X-ray infiltrates, Creactive protein, leucocytes count, and recovery of a pathogen from the respiratory tract or from blood cultures. However, they are all non-specific symptoms and hence differentiation between viral and bacterial ARTI remains a diagnostic challenge(7),(8).

A novel approach to guide antimicrobial therapy is to prescribe antibiotics based on the level of biomarkers, specifically, calcitonin precursors, including PCT. Circulating levels of PCT are elevated in systemic bacterial infections but remain relatively low in viral infections and inflammatory diseases(9),(10). In severe bacterial infections the use of PCT significantly improves the sensitivity and specificity of the clinical diagnosis of infection(11).

A large number of publications, primarily clinical studies, demonstrate the increasing use of PCT in modern clinical practice. PCT is a propeptide of calcitonin induced by a variety of stimuli including bacterial endotoxins, proinflammatory cytokines and triggering events such as trauma or cardiogenic shock. PCT is not or only slightly induced by viral infections, autoimmune disorders, neoplastic disease and organs transplantation(12). The aim of this study was to evaluate the usefulness of PCT as a diagnostic and prognostic tool in patients for early differentiation between bacterial and nonbacterial infection origin and to compare its utility with the other markers of infection as leucocyte count mainly neutrophil and C reactive protein concentration. In the present work 110 children participated in 4 groups, the control group included 20 apparently healthy children; the diseased children classified 30 in each. They were pharyngotonsillitis, acute rhinosinusitis and acute otitis media. Blood, postnasal discharge and swab from the air were cultured to detect the bacterial cause of infection and ELIZA technique was used to detect Adeno and R.S.V antigen. The following was reported, bacterial infection (positive culture) in: 16 cases of pharyngotonsillitis, 14 children of acute Rhinosinusitis and 13 children with acute otitis media. The rest were in viral infection of adenovirus is represented in 69.8% of them (30 children) and R.S.V in the other 30.2%.

Early detection of microbial infection is necessary, however bacterial culture are either negative under antibiotic treatment or need some days to indicate the growth of mi-
crobiocal agents. Also microbiological cultures may be negative if sepsis is not restricted to the presence of a known or clinically detectable infectious focus\textsuperscript{(13),(14)}.

In our study the plasma procalcitonin level was significantly higher in bacterial infection (6.9 ± 16.3) than its level in viral infection (0.9 ± 2.8) and its level in control group (0.1 ± 0.4). We point that concentrations > 2ng/ml of procalcitonin has 100% sensitivity and specificity of > 97%.

With the same cut off value of PCT (2ng/ml), Hatherill et al., (1999)\textsuperscript{(14)} obtained the same values of sensitivity and negative predictive value for sever bacterial infection (100%) as our levels but with lower specificity and positive predictive value 70% and 78% respectively.

Similar results to our were reported by Chiesa et al., (1998)\textsuperscript{(15)} for sensitivity and specificity of PCT (92.6% and 97.5% respectively) when used to identify early neonatal sepsis.

In our study CRP had sensitivity 96.1% but its specificity was 85%. In other study by Bernard et al.,\textsuperscript{(16)} CRP sensitivity was 97% CRP specificity and PPV can be explained by presence of 15% false positive cases, while PCT has no false positive cases. Other advantage of PCT over CRP in sepsis diagnosis is the early elevation of PCT more than CRP as PCT concentrations start to rise from about four hours, peak at about six hours, and remain increased for over 24 hours. In contrast, CRP concentrations begin to rise between six and 12 hours.

So CRP response is not specific and can never by its own be diagnostic. This agrees with those of Muller (2000)\textsuperscript{(17)} and colleagues who revealed that procalcitonin level was more reliable marker of sepsis than is C-reactive protein, IL-6 and lactate. Hatherill, et al. (1999)\textsuperscript{(14)} Observed that admission of procalcitonin was significantly higher in children with septic shock (median 94.6; range 3.3-79.8ng/ml) compared with localized bacterial infection (2.9; 0-24.3 ng/ml), viral infection (0.8; 0-4.4ng/ml), and controls (0; 0-4.9ng/ml).

Our study revealed that the median plasma C reactive protein were significantly higher in localized bacterial infections 32 ± 13.8 than in viral infection (12 ± 7.1) and control group (5.1 ± 1.8). This coincide with the study done by Moulin et al (2001)\textsuperscript{(18)} who showed CRP concentration of 20mg/l has a similar sensitivity but a much lower specificity than PCT (40%, 86%) for discriminating between bacterial and
viral causes of pneumonia. Our study revealed no statistical significant difference in total leucocytic count in the studied groups. Our data support the view of some authors that the leucocytic count has little value in differentiation (the mean of TLC was 10.1 ± 5.8, 19.1 ± 6.8 and 12.1 ± 7.3 respectively in the control, bacterial and viral groups). Our study illustrates the superior sensitivity and specificity of procalcitonin compared with C reactive protein and WBCs. That agrees with those of Moulin et al who revealed that, PCT concentration differentiated viral and bacterial infections more effectively than CRP, IL-6, or WBCs counts.

Carrol et al., (2002)\(^{19}\) describe PCT as a marker of bacterial sepsis, they found that it's high concentrations correlate with the severity of sepsis and it has been proposed as an earlier and better diagnostic marker than CRP and white cell count.

Another studies support the notion that the course of PCT concentrations rather than the absolute height is a mirror of the systemic inflammatory response and plays major role for prognosis. In successfully treated infections, circulating PCT levels decrease in a log-linear pattern and have a plasma half life of 24 hours. In contrast, prolonged elevated plasma PCT levels indicate adverse outcome. A concentration of procalcitonin > 2ng/ml had 100% sensitivity and negative predictive value for bacterial infection\(^{20}\).

Unnecessary antibiotic use (i.e. number of prescriptions and duration of treatment) for ARTI not only increases drug expenditure and the risk of adverse events, but also results in selection of resistant microorganisms. Thereby, it constitutes an important public health problem. For combating the increase in resistant infections a decrease of the excess antibiotic use is paramount \(^{21},^{22}\).

Our review of the available literature on the subject enables us to state the following: Serum PCT levels increased significantly only in bacterial respiratory tract infections. Increases in serum PCT concentration were related to the intensity of systemic inflammatory response in the course of disease. Measurements of PCT concentrations were useful in clinical decision making as to antimicrobial treatment. Testing the serum PCT level not only supplements the range of available markers of "acute phase" response, but also provides some additional information about on going systemic inflammatory\(^{23,24}\).

Conclusion:

The admission procalcitonin con-
centration has better sensitivity, specificity, and predictive value for bacterial infections than either C-reactive protein or the leucocytic count. Procalcitonin provide the clinician with a useful addition to currently available investigations, although given the poor performance of the leucocytic count and to a lesser extent C reactive protein, it might even be argued that the routine use of these tests in motivated more by low cost, easy availability, and historical practice rather than diagnostic value. We suggest that procalcitonin measurement has the potential to shorten the duration of both antibiotic treatment and hospital stay.

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