Introduction:
Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease. It is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. COPD is a chronic inflammatory disease. It may cause hospital admissions with acute exacerbations in those who do not receive regular treatment or even in those who do as a result of intervening pulmonary infection. Guidelines from the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) recommend antibiotics for the treatment of moderate to severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) with viral infection. Accurate methods to differentiate viral and bacterial respiratory infections to allow targeted antibiotic therapy would be beneficial. Acute phase reactants are capable of demonstrating the inflammation; however, they are not employed to make a difference between bacterial and nonbacterial causes of the inflammation. Recently, measurement of procalcitonin (PCT) levels appears to be useful in order to minimize this problem.

Key words: AECOPD, PCT

Acute exacerbation of COPD (AECOPD)

The American Thoracic Society (ATS) and European Respiratory Society (ERS) define an exacerbation as a change in a patient’s baseline dyspnea, cough, or sputum that is beyond normal variability, and that is sufficient to warrant a change in therapy. AECOPD was considered bacteriologically confirmed in the presence of a positive Gram stain of respiratory samples, a pathogen concentration greater than 10^5 cfu/ml in tracheobronchial aspirations, a blood culture revealing a bacterial pathogen in the absence of an extra pulmonary focus, or positive serological tests.

Microbial pathogens in COPD exacerbation

The list of potential pathogens in COPD exacerbations includes typical respiratory bacterial pathogens, respiratory viruses and atypical bacteria (Table I). Among the typical bacteria, Nontypeable Haemophilus Influenzae (NTHI) is the most common and its role in COPD is the best understood. A high prevalence of respiratory viruses has been reported in severe AECOPD requiring ventilation. Among the viruses, Rhinovirus and Respiratory Syncytial Virus (RSV) have received considerable attention in recent years.
Differentiating diagnostic tools in AECOPD:

Classical diagnostic instruments including CRP and leukocyte count do not have sufficient specificity in differentiating between bacterial infections, noninfectious systemic inflammations or viral infections. Recently, serum procalcitonin (PCT) has been used as an infection marker. Since the extent and severity of infection gradually increase in bacterial infections, serum PCT levels have also been shown to increase. There is even a specific cut-off value for PCT for the establishment of a bacterial infection.

Procalcitonin (PCT) is a peptide precursor of hormone calcitonin, the later being involved with calcium homeostasis. It is composed of 116 amino acids and is produced by the parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine. The level of procalcitonin raises in response to a proinflammatory stimulus, especially of bacterial origin. Serum PCT levels are detectable as early as 3–4 hours after the invasion, which is much earlier than the increase in the C-reactive protein level or erythrocyte sedimentation rate. Available data indicate that PCT levels are not influenced by therapy with glucocorticoids or nonsteroidal anti-inflammatory agents. PCT levels do not increase or increase only modestly in patients with infection due to respiratory viruses.

In healthy humans, its normal serum level is 0.1 ng/ml. In serum, procalcitonin has a half-life of 2.5 to 30 hours. Elevated serum concentrations of PCT was initially detected in patients with sepsis and infection. Hyperprocalcitonemia appears within 2 to 4 hr in patients with infection, often reaches peak values in 8 to 24 h, and then persists as long as the inflammatory process continues. With recovery, PCT levels return to normal. The sensitivity and specificity of PCT in bacterial infections were found to be 92.6% and 97.5%, respectively. In delayed bacterial infections (3-30 days), the sensitivity and specificity reached 100%. Serum PCT level above 0.5 ng/ml indicates bacterial infections, whereas levels above 2 ng/ml show sepsis. When the threshold level of PCT indicative of bacterial infection was accepted as 0.5 ng/ml, the positive and negative predictive values were found to be 100% and 87%, respectively. PCT measurements may also be used to reveal the disease severity.

Serum IFN-c levels increase in response to a variety of viral respiratory tract infections. Thus, the absence of an increase in serum PCT levels in patients with viral respiratory tract infection may be due to inhibition of PCT synthesis by IFN-c. In contrast, there are substantive data that human infection with rhinovirus, respiratory syncitial virus (RSV), influenza, adenovirus, and metapneumovirus stimulate a robust cytokine response.

### Table I: Microbial pathogens in exacerbations of COPD

<table>
<thead>
<tr>
<th>Pathogen class</th>
<th>Proportion of exacerbations</th>
<th>Specific species</th>
<th>Proportion of class of pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>40%–50%</td>
<td>Nontypeable <em>Haemophilus influenza</em></td>
<td>30%–50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
<td>15%–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Moraxella catarrhalis</em></td>
<td>15%–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Pseudomonas spp.</em> and <em>Enterobacteriaceae</em></td>
<td>Isolated in very severe COPD, concomitant bronchiectasis, recurrent exacerbations</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Haemophilus parainfluenzae</em></td>
<td>Isolated frequently, pathogenic significance undefined</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Haemophilus hemolyticus</em></td>
<td>Isolated frequently, pathogenic significance undefined</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td>Isolated infrequently, pathogenic significance undefined</td>
</tr>
<tr>
<td>Viruses</td>
<td>30%–40%</td>
<td><em>Rhinovirus</em></td>
<td>40%–50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Parainfluenza</em></td>
<td>10%–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Influenza</em></td>
<td>10%–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>RSV</em></td>
<td>10%–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Coronavirus</em></td>
<td>10%–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Adenovirus</em></td>
<td>5%–10%</td>
</tr>
<tr>
<td>Atypical bacteria</td>
<td>5%–10%</td>
<td><em>Chlamydia pneumoniae</em></td>
<td>90%–95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
<td>5%–10%</td>
</tr>
</tbody>
</table>
response that includes gamma interferon28,30. Furthermore, the magnitude of the IFN-γ response varies with the type of inciting virus (eg, IFN-γ levels are higher in nasopharyngeal secretions obtained from patients with influenza than in RSV-infected patients29.

**PCT Guidance of antibiotic therapy**

It has always been difficult to decide whether to start antibiotics in patients admitted with COPD exacerbations. Complaints of the patients (increased cough, increased sputum purulence, increased shortness of breath, high fever etc), radiological examinations, and laboratory measurements help clinicians in this respect. PCT measurements, on the other hand, may enable clinicians to distinguish bacterial infections from non-bacterial ones and may make the antibiotic decision easier with an increased confidence. In a recent study, there was a highly statistically significant difference (p-value <0.001) between AECOPD patients on one side and stable COPD patients and healthy control subjects on the other side regarding the mean values of PCT31 (Table II).

<table>
<thead>
<tr>
<th>Groups</th>
<th>PCT Mean ± SD (ng/ml)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AECOPD patients</td>
<td>1.44 ± 0.542</td>
<td>1 vs 2 &lt; 0.01</td>
</tr>
<tr>
<td>2. Stable COPD patients</td>
<td>0.05 ± 0.012</td>
<td>1 vs 3 &lt; 0.01</td>
</tr>
<tr>
<td>3. Control subjects</td>
<td>0.04 ± 0.010</td>
<td>2 vs 3 &gt; 0.05</td>
</tr>
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</table>

In a study by Tasci et al, the mean serum PCT levels in COPD exacerbations were 1.8 ng/ml and in stable COPD patients was 0.2 ng/ml32. Mohamed and his colleagues found the levels of PCT for patients of group A (bacterial exacerbated COPD) (2.69 ± 0.62 ng/ml) were significantly higher than group B (non bacterial exacerbated COPD) (0.07 ± 0.02 ng/ml) and control group (0.05 ± 0.02 ng/ml) (p<0.001)33. Pazarli et al discovered that mean levels of PCT in AECOPD were significantly higher than COPD in stable conditions34. In another study by Zhang Y and his colleagues, before treatment, the levels of PCT in the infective COPD group were significantly higher than that in the non-infective group (p<0.01). In the infective group, the levels of PCT after the treatment were much lower than those before treatment (p<0.05)35. Tanriverdi et al, found that the mean PCT levels were significantly higher in COPD patients with positive sputum cultures than in patients with negative sputum cultures36.

It has been demonstrated antibiotics have a marginal efficacy in the treatment of AECOPD, except among patients with evidence of bacterial infection or severe exacerbation37. Less than 50% of severe AECOPD may be attributed to bacteria, suggesting the potential for excessive antibiotic use in this setting38. Therefore, serum procalcitonin level may be considered as a useful tool for predicting bacterial infection, and may prove useful for selecting patients with a lower probability of bacterial infection and limit the inappropriate use of antibiotics, specifically in the ICU setting where antibiotic use and the emergence of antimicrobial resistance are highly prevalent39. This suggests that COPD exacerbations with a high PCT value may be a result of a bacterial infection even if a bacterial growth is absent, and antibiotic use is mandatory in these patients. In this context, we speculate that antibiotic use in the subgroup of severe AECOPD with lower PCT (< 0.1 μg/L), could be reduced also.

Despite many studies demonstrating marginal efficacy for antibiotic therapy in COPD, 85% of patients with COPD exacerbations are treated with antibiotics40. In addition, despite the fact that lower respiratory tract infections (LRTI) are frequently due to viral infections, up to 75% of these patients seen in general medical practices are treated with antibiotics41. Current guidelines recommend antibiotic therapy for most patients with acute exacerbation of COPD of 3 to 7 days42. Thus, it is widely agreed that antibiotics are overprescribed. This misuse of antibiotics can be harmful in two ways: patient-specific side effects from treatment and population-based adverse events related to development of bacterial resistance.

**Conclusion:**

Nevertheless, we can conclude that PCT-guided antibiotic therapy in patients with AECOPD is likely to reduce antibiotic use and exposure without a detrimental effect on patient safety.

**References:**
