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Cover Story:

COVID-19
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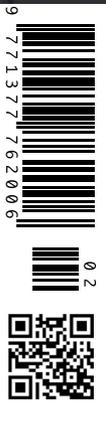
The Role of Procalcitonin for Risk Assessment and Treatment of COVID-19 Patients

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Procalcitonin is widely used to assess the risk of bacterial infection and disease progression. Can it be an additional tool to identify COVID-19 patients at risk of severe disease?

☑ Key Points

- Procalcitonin (PCT) is a widely used biomarker to assess the risk of bacterial infection and disease progression.

- Early evidence suggests that PCT may also be a valuable tool in identifying COVID-19 patients at high risk for clinical deterioration or patients at risk for bacterial co-infection.

- PCT helps to discriminate between milder cases and more severe cases. PCT also helps to distinguish between severe bacterial pneumonia and mild viral pneumonia.

- If a patient has bacterial co-infection, his prognosis and his mortality risk increases if early antibiotic treatment is not initiated.

- Recent clinical findings show that unnecessary antibiotic use can be safely reduced in patients with low likelihood of bacterial co-infection indicated by low PCT values.

COVID-19 and Procalcitonin

Procalcitonin (PCT) is a widely used biomarker to assess the risk of bacterial infection and disease progression. In patients with bacterial sepsis, suspected or confirmed lower respiratory tract infections, including community-acquired pneumonia, acute bronchitis and acute exacerbations of COPD, PCT can be a useful decision-making tool for antibiotic therapy (Schuetz et al. 2018). In addition, early evidence suggests that PCT may also be a valuable tool in identifying COVID-19 patients who may be at risk for bacterial co-infection.

COVID-19 is a respiratory and systemic disease that has infected millions of people worldwide. Most patients experience a mild form of the disease but there is a certain percentage of patients who progress to a very severe disease state that requires intensive care and invasive ventilation. In order to ensure better patient management and improved outcomes, early identification of patients who may be at a higher risk of severe infection can play an important role.

COVID-19 is a relatively new disease, and there is still a lot we don't know about it. While we still need more reliable data, evolving evidence suggests that the use of PCT can help physicians better manage patients with COVID-19. We already know that in all the types of infections from the lung such as bacterial pneumonia or other types of viral pneumonia, PCT helps to discriminate between milder cases and more severe cases. PCT also helps to discriminate between severe bacterial pneumonia and mild viral pneumonia.

Most COVID-19 patients have very low PCT levels (<0.25μg/L or even <0.1μg/L) at the time of admission, but elevated markers of inflammation such as white blood count (WBC) and C-reactive protein (CRP) indicate that they have inflammation in the lung. However, at a certain point, in the course of the disease, their PCT

levels start to increase. This could be due to two reasons. One of them would be that the patient has acquired bacterial co-infection. This is common in patients with a viral infection because once the lung tissue gets damaged by the virus, it's easier for normal bacterial flora to gain access and become invasive. This results in the development of secondary bacterial pneumonia in these patients, which is typically confirmed through blood cultures, sputum tests and radiological confirmation. If these tools show signs of bacterial pneumonia, it's very important to start antibiotic treatment in these patients. If a patient has bacterial co-infection, his prognosis and mortality risk increases if early antibiotic treatment is not initiated

The other reason could be that a patient starts to deteriorate, his general condition becomes much worse, he

can be a useful prognostic marker as information about PCT levels can give clinicians the confidence that the disease is not at a very severe stage. On the other hand, if PCT levels are high, this could be an indicator that the patient's condition has become severe either because of a co-infection or because of inflammation.

Determining Bacterial Co-Infection: PCT and Other Biomarkers

There are two possibilities when determining co-infection. One would be to look at the host, i.e. the patient, and the second would be to look at the pathogens. PCT is a host driven marker. If PCT goes up, it is a strong indicator that the host has a problem. PCT is a much more potent tool compared to other inflammatory markers such as CRP or white blood count because these are

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Bacterial co-infection is common in patients with a viral infection because once the lung tissue gets damaged by the virus, it's easier for normal flora bacteria to gain access and become invasive

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goes into shock and develops an inflammatory syndrome – a COVID associated pneumonitis, which has a complex pathophysiology with endothelial dysfunction. During this severe inflammation and septic illness, there is also translocation of bacteria through the gut membranes and a very strong induction of different cytokines. This increases PCT production by bacterial translocation through the intestines but also directly because of the huge inflammatory boost and toxic syndrome that is developing in these patients.

Overall, if a patient has milder COVID-19 infection, they generally are expected to have low PCT levels. This also confirms that it is not a bacterial infection but a viral infection. However, if, during the course of the disease, the patient gets worse, and his PCT levels increase, it must be taken seriously. This does not necessarily mean that there is bacterial co-infection. That could be a possibility, but it could also mean that the patient is going into severe inflammatory pneumonitis syndrome. In such cases, treatment strategies such as corticosteroids may be considered. However, PCT in these patients can function as a marker to monitor the patient and provide feedback on what's going on in the body of these patients. If a patient comes in with mild disease and low fever, PCT levels are expected to be low. In patients who self-quarantine at home and did not come to the hospital, and if their condition gets worse, PCT

inflammatory markers and are already increased in most of these patients due to inflammation.

PCT is a better marker because it's much more specific towards bacterial infection. However, high PCT levels alone do not prove there is co-infection. Once there is a patient with high PCT, there is still a need to look at pathogen derived markers such as PCR, sputum culture etc. This can help prove what type of infection it is because there could be different types of bacteria causing the problem.

The effectiveness of PCT as a prognostic tool for lung infection and for respiratory tract infections has already been proven in several studies. There is also strong indication of its benefits in COVID-19 patients, but since this is a new disease, the evidence is still evolving. While we may not have strong data at the moment, more studies show that PCT has significant prognostic implications (Gregoriano et al. 2020), and it can help detect co-infection. Based on the Wuhan cohort, and also some data from Italy and the U.S., the recommendation is to look at D-dimer levels to determine endothelial dysfunction and vascular problems. However, PCT is being used in addition to other prognostic tools, for the purpose of monitoring patients and as an infection marker.

PCT and Antibiotic Treatment
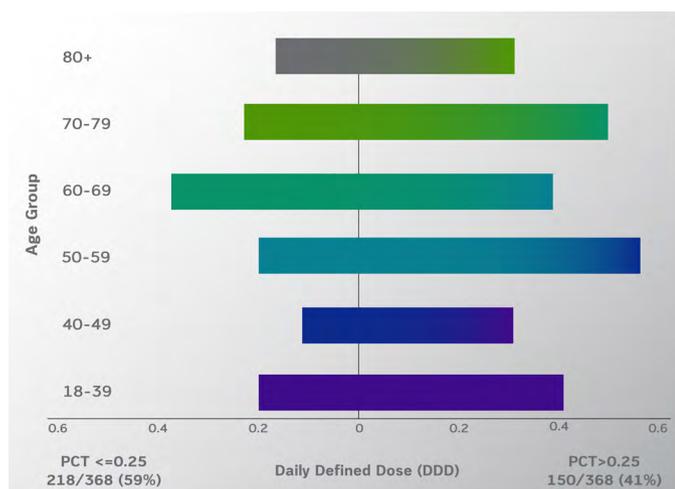Evolving data show that more than 70% of COVID-19 patients

Figure 1: Antibiotic use (DDD) in COVID-19 patients treated in line with a PCT-based guideline recommending to limit antibiotic treatment to patients with PCT >0.25μg/L , if not indicated otherwise by clinical assessment. (Adapted from Williams et al. 2020)

get antibiotic treatment as it can be a challenge to identify COVID-19 patients without bacterial co-infection in whom antibiotics could be stopped safely. However, recent clinical findings show that procalcitonin can help in the assessment of these patients and reduce unnecessary antibiotic usage (Williams et al. 2020) (Fig.1).

Once a bacterial co-infection is established in a COVID-19 patient, PCT is very helpful to also monitor the patient and guide treatment duration. Typically, if there is a patient with high PCT levels and if co-infection is confirmed, it is important to bring PCT levels down by about 50% every other day. If the levels do not drop, it would suggest that the treatment is not working. Hence, PCT is a very useful marker. If PCT levels drop, it would indicate that the treatment is working and that the patient is on track. Once the levels have dropped substantially – around 80 to 90% of the peak level - it is safe to stop antibiotic treatment. This way, PCT is also a great tool to guide antibiotic treatment and can help reduce the unnecessary usage of antibiotics. PCT is an excellent marker that gives clinicians feedback on the course of the disease and how well treatment is working.

PCT is routinely used in our treatment setting, and we have evidence that PCT has strong prognostic implications. While Switzerland did not have thousands of patients as in other countries, but still in the patients that we treat, we use PCT, and we have clinical evidence that it is an effective tool for COVID-19 patients (Gregoriano et al. 2020).

COVID-19 is a healthcare challenge that has shaken most healthcare systems around the world. When it first started in China, other countries underestimated the severity of the disease and the implications of this infection. Now we know that this virus is causing very high severity of disease and significant morbidity and mortality. We also know a little bit

more about treatments and have a better idea as to how to diagnose patients and how to treat them. Prevention by social measures is now the main focus with different countries having different preventive measures in place. It is hoped that we will continue to see a drop in cases, and this pandemic will pass. Things remain uncertain as to how the next month will be with COVID-19 and whether we will continue to see cases in the coming months or whether we will be able to get the situation under control globally. Only time will tell, but for now, we can continue to do our best and diagnose, treat and manage COVID-19 patients to the best of our ability.

Obviously, the COVID-19 infection is far too heterogeneous and complex to be reduced to a single cut-off of any biomarker. Still, current evidence suggests that the likelihood for an adverse course with pneumonitis and/or bacterial co-infection increases with increasing serum levels of PCT. Knowledge of assay characteristics, particularly the functional assay sensitivity, and strengths, pitfalls and optimal cut off ranges in a predefined clinical settings are prerequisites for its optimal use in clinical routine. Importantly, PCT levels must always be evaluated in the context of a careful clinical and microbiological assessment. As the kinetics of PCT is of particular diagnostic and prognostic interest, repeated measurements should always be performed in the inhospital setting. In addition, immuno-modulating drugs may suppress the upregulation of different biomarkers including CRP, and increase levels of WBC. PCT seems to be less affected by steroid use, but again more research is needed to better understand how different treatments for COVID-19 may influence PCT levels. ∎

B·R·A·H·M·S PCT

B·R·A·H·M·S PCT provides information on the presence and severity of bacterial infection, helping clinicians in the intensive care unit, emergency department, and other hospital wards decide whether to initiate antibiotic therapy in patients with suspected or confirmed lower respiratory tract infections (LRTI) and when to safely discontinue antibiotics in patients with LRTI and sepsis. Clinicians in health systems worldwide rely on B·R·A·H·M·S PCT since 1996 to make patient care decisions with confidence. More than 5,500 publications have demonstrated the clinical utility of PCT, defined clinical cut-offs, and treatment algorithms based on the B·R·A·H·M·S PCT assay performance.

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