Cover Story:

# COVID-19 Management
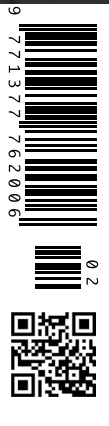
# B·R·A·H·M·S PCT: A Valuable Tool for Bacterial Coinfection Risk Assessment

## Procalcitonin – A Critical Biomarker

Procalcitonin (PCT) is a member of the calcitonin family and known as a critical biomarker for bacterial infections. To be effective a biomarker must have high diagnostic accuracy and allow early and rapid diagnosis. PCT fulfills these requirements and has already demonstrated superior diagnostic accuracy compared to other conventional biomarkers (Müller B. et al., 2000; Meisner M., 2010)

PCT is widely used for the differential diagnosis of bacterial infection and risk assessment for progression to severe sepsis and septic shock. In addition, change in PCT over time is used to assess the response to therapy and determines the mortality risk in patients with bacterial sepsis. Moreover, PCT is also a critical tool to facilitate decisions regarding antibiotic therapy in patients with suspected or confirmed lower respiratory tract infections (LRTI), including community acquired pneumonia (CAP), acute bronchitis and acute exacerbations of COPD (AECOPD) (Schuetz P. et al., 2018).

As a marker reflecting the systemic response to a bacterial infection, procalcitonin is usually low in viral infection (Meisner M., 2000). This has been proven also during viral epidemics like H1N1 influenza (Ingram P.R. et al., 2010; Cuquemelle E. et al., 2011, Rodriguez A.H. et al, 2016), SARS (Chua A. & Lee K.H., 2004) or MERS (Rhee J.Y. et al, 2016). In case of bacterial coinfection, though, PCT was found to be a valuable tool to differentiate pure viral disease from bacterial (co)infection where elevated PCT levels were observed and higher severity of disease was reported (Guan W. et al., 2020; Karhu J. et al., 2019; Pavia A.T. et al., 2013). A PCT below 0.5µg/L was shown to have a high negative predictive value to exclude presence of bacterial coinfection (Rodriguez et al., 2016)

## Procalcitonin and COVID-19 Patients

Coronavirus disease 2019 (COVID-19) is a new respiratory and systemic viral disease that has already infected millions of people globally. Although most of the infected patients experience a mild form of the disease, a smaller percentage progresses to very severe disease state requiring intensive care and invasive ventilation (Chen N. et al., 2020; Chen R. et al, 2020; Guan W. et al, 2020; Zhou F. et al 2020;). An early identification of these patients at elevated risk or evolving disease would be critical to improve patient management and outcome.

Unfortunately, on admission neither radiological findings and clinical symptoms nor white blood count (WBC) or C-reactive protein (CRP) seem to be predictive for severity and outcome risk, as these parameters were elevated also in a majority of patients with mild disease and non-adverse outcome (Guan W. et al., 2020).

On the other hand, the descriptive studies revealed that procalcitonin on admission was usually low in patients with mild disease and non-adverse outcome, with only less than 4% of those patients having elevated PCT value (Guan W. et al., 2020). Also other available study data indicate that procalcitonin could be a valuable tool in the current COVID-19 pandemic for early identification of patients at risk for bacterial coinfection and adverse outcome (Huang et al. 2020; Guan et al. 2020; Zhou et al. 2020; Chen N. et al. 2020; Xiao-Wei et al. 2020, AACC 2020).

Accordingly, in a meta-analysis of 4 studies, elevated PCT was found to indicate a nearly fivefold higher risk for severe disease (Lippi and Plebani, 2020; AACC 2020). The authors
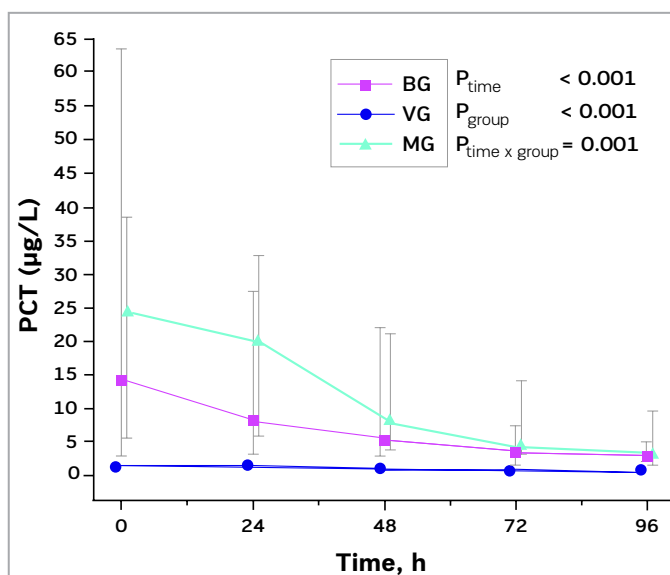


Fig.1: Procalcitonin (PCT) concentrations over time for patients with pure viral infection (VG), bacterial infection (BG) or mixed (viral with bacterial coinfection MG) during an H1N1 influenza epidemic; adapted from Karhu J. et al., Cytokine 2019, 113:272-27
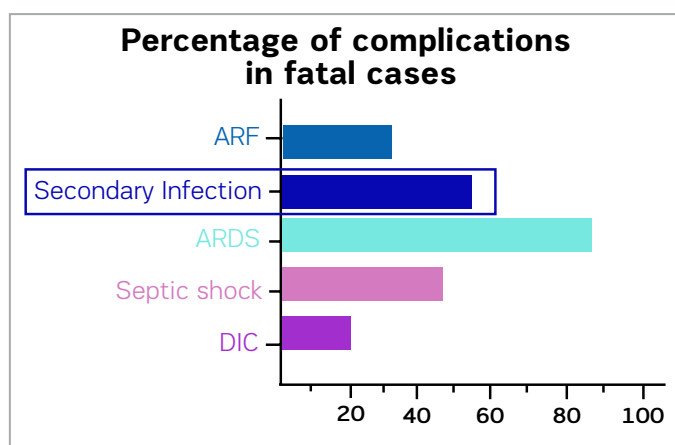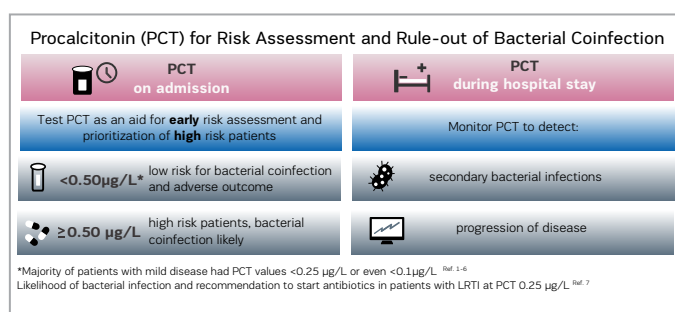
Fig.2 Percentage of complications in fatal cases out of 1590 hospitalized patients across China (adapted from Chen R. et al., 2020) ARF: Acute Renal Failure; ARDS: Acute Respiratory Distress Syndrome; DIC: Disseminated Intravascular Coagulation



Procalcitonin (PCT) for Risk Assessment and Rule-out of Bacterial Coinfection

linked this to the potential contribution of secondary (bacterial) infection and concluded that a serial testing of PCT could be helpful to identify deteriorating patients timely.

This is further supported by the analysis of 1590 patient cases from whole China (Chen R. et al. (2020) which found that in those patients with fatal outcome, besides ARDS, the most frequent complications were secondary infections and septic shock (Fig.1) and that procalcitonin >0.5µg/L was the strongest outcome predictor with a hazard ratio of 8.72 (see table 1).

Based on the available evidence on PCT and COVID-19, procalcitonin is included in a variety of COVID-19 related guidelines and recommendations like, e.g. by IFCC or CDC to assess likelihood of bacterial coinfection which would be associated with a higher outcome risk (IFCC 2020; CDC 2020).

Procalcitonin could be helpful in limiting overuse of antibiotics in patients with COVID-19 related pneumonia. Although the bacterial coinfection rate in the overall population is very low, which is also reflected by low PCT values in the majority of patients, more than 70% of patients got antibiotics for 3-17 days (Huang C. et al., 2020; Chen W. et al., 2020).

Based on the available evidence for PCT as an effective

| Variable | Level | Hazard Ratio (HR) | 95% CI |
|---|---|---|---|
| Age, years | 65-74 vs <65 | 3.43 | 1.24 - 9.5 |
| Age, years | >75 vs <65 | 7.86 | 2.44 - 25.35 |
| Coronary Heart Disease (CHD) | Yes vs No | 4.28 | 1.14 - 16.13 |
| Cerebro-Vascular Disease (CVD) | Yes vs No | 3.1 | 1.07 - 8.94 |
| Dyspnea | Yes vs No | 3.96 | 1.42 - 11.0 |
| Procalcitonin (PCT); µg/L | >0.5 vs <0.5 | 8.72 | 3.42 - 22.28 |
| Aspartate Amino-Transferase (AST); U/L | >40 vs <40 | 2.2 | 1.1 - 6.73 |

Table 1: Independent outcome predictors per multivariate Cox regression (adapted from Chen R. et al., CHEST 2020)

and safe aid in antibiotic stewardship of lower respiratory tract infections (Schuetz P. et al., 2011) and the association of low PCT levels and mild COVID-19 disease course, it was recommended that in case of repeatedly low PCT antibiotic treatment should be stopped in COVID-19 patients.

For example, J.P. Metlay and G.W. Waterer, the co-chairs of the ATS and IDSA CAP guidelines, provide their interpretation for the use in COVID-19 patients and point out that they "…endorse the use of a low procalcitonin value early in the course of confirmed COVID-19 illness to guide the withholding or early stopping of antibiotics, especially among patients with less severe disease…"

Similarly, UK specialists in a knowledge-sharing session

on ICU management of COVID-19 patients concluded to use PCT as a "stop signal" to guide when to stop antibiotics use and to monitor patients for bacterial infection and restart antibiotics when required (NIHR, UCL partners & ICS, 2020). Accordingly PCT-based algorithms were introduced into hospital protocols (Brighton and Sussex University Hospitals, NHS, UK, 2020) (see Fig. 3).

## Guidelines on the use of Procalcitonin in COVID-19



Procalcitonin (PCT) is a sepsis biomarker. It does not significantly increase in COVID-19 unlike CRP so can help along with clinical assessment with diagnosing/ ruling out superimposed bacterial infection for COVID patients, and to guide the initiation and cessation of antibiotics.
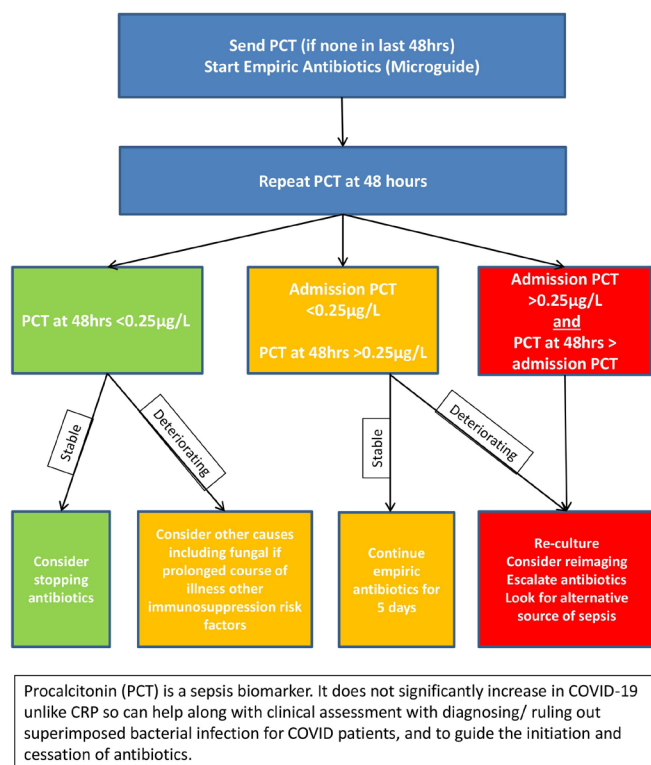
Figure. 3: PCT algorithm for use in COVID-19 patients as part of the hospital guideline of Brighton and Sussex University hospitals, NHS, UK. Source: bsuh.nhs.uk/library/wp-content/uploads/sites/8/2020/04/Covid107.1_Guidelines-on-the-use-of-Procalciton-in-in-COVID-19-REDO-9.4.pdf

## ✓ Key Points

- PCT testing is an important tool to differentiate bacterial infection from other causes of inflammation and to aid in antibiotic stewardship. Current evidence shows that PCT may also be an effective aid in COVID-19 patients

- Low PCT can be helpful to early identify patients with low likelihood of bacterial coinfection and severe disease, and aid in stopping antibiotic treatment

- PCT monitoring should be done routinely also in COVID-19 patients to detect and treat superinfection timely

- PCT can aid in targeted antibiotic treatment and monitoring of treatment response

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. In conjunction with other laboratory findings and clinical assessments, B·R·A·H·M·S PCT provides valuable information on the severity of a bacterial infection – both on presentation and during the course of treatment of the septic patient. 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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