Biomarkers for antimicrobial stewardship: a reappraisal in COVID-19 times?

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On initial presentation, differentiation between early-stage coronavirus disease 2019 (COVID-19) and classical bacterial community-acquired pneumonia can be challenging. Furthermore, COVID-19 patients may develop a hyperinflammatory phase later in their disease process, which is particularly difficult to distinguish from a secondary bacterial infection. As a consequence, 72% of COVID-19 patients receive empirical antibiotic therapy during hospital stay [1]. Antibiotic overuse undoubtedly leads to an exacerbation of another—slowly progressive—pandemic: antimicrobial resistance [2].

Procalcitonin (PCT) has proven useful in the early diagnosis of lower respiratory tract infections of bacterial origin [3]. Furthermore, in the ICU setting, serial measurement of PCT can safely guide the withdrawal of antibiotic therapy [4].

In patients with COVID-19, C-reactive protein (CRP) is usually increased on presentation while PCT is often low [5]. PCT appears to increase in COVID patients with severe disease and/or in those presenting with secondary bacterial infections [6]. Longitudinal data on both biomarkers in COVID-19 infections are currently lacking. Also, it is unclear to what extent PCT and CRP predict the occurrence of secondary infections in these patients.

Data from 66 COVID-19 ICU patients were recorded in the Good Clinical Practice (GCP)-compliant data management system Castor (Castor EDC, Amsterdam, The Netherlands). PCT was determined using the Elecsys BRAHMS procalcitonin assay (Thermo Fisher Scientific), whereas CRP was determined using an immunoturbidimetric assay, both on a Cobas 8000 immunoanalyzer (Roche Diagnostics). Secondary infection was defined as “any infectious episode” evidenced by the presence of positive cultures and time-stamped at the day the culture was performed. Infectious episodes were independ-
ently determined by two ICU physicians (JS and HT). In case of incongruency, a third ICU physician (PP) was consulted. In case of multiple secondary infections, only the first infectious episode was analyzed.

Half of the patients \((n = 33)\) developed a secondary infection during ICU admission. No significant differences in characteristics were observed between patients who did or did not develop a secondary infection (Table 1). In patients without secondary infection, both PCT and CRP decreased over time (Fig. 1a), with PCT values lower \((\text{peak geometric mean [95% CI]} \: 0.64 [0.32–1.27] \, \mu g/L)\) than CRP \((\text{peak geometric mean [95% CI]} \: 192 [107–342] \, \text{mg/L})\) compared to their respective cutoff values for bacterial infection \(< 0.5 \, \mu g/L \text{ and } < 100 \, \text{mg/L, respectively}\). A significant increase in both PCT and CRP levels was observed in case of the occurrence of a secondary infection (Fig. 1b). The receiver operating curve analysis of PCT and CRP yielded AUCs of 0.80 and 0.76, respectively (Fig. 1c). In patients with PCT \(< 0.25 \, \mu g/L\), the negative predictive value was 81%, whereas PCT levels of \(> 1.00 \, \mu g/L\) had a positive predictive value of 93%. Intermediate PCT levels were of limited diagnostic value. For CRP, predictive values were less robust (Fig. 1c).

The use of biomarkers to predict secondary infections in ICU patients warrants reappraisal in times of COVID-19. We demonstrate that COVID-19 patients who do not develop a bacterial infection present with high initial CRP levels and low-moderate PCT levels that gradually decrease over time. Furthermore, our data show that, during ICU admission, PCT levels of \(> 1.00 \, \mu g/L\) rule in, whereas concentrations of \(< 0.25 \, \mu g/L\) rule out secondary bacterial infections with good predictive values.

With regard to ICU antimicrobial stewardship, initiation of empirical antibacterial therapy in ICU patients with low PCT levels should probably not be started. As CRP is consistently elevated, this biomarker does not have predictive value for bacterial infections in the initial phase of COVID-19. Later on during ICU stay, serial PCT and, to a lesser extent, CRP may help to identify or rule out nosocomial bacterial infections and prompt appropriate use of antibiotic therapy.

| Table 1 Patient characteristics |
|--------------------------------|
| **Sex** | Secondary infection \((n = 33)\) | No secondary infection \((n = 33)\) | \(p\) value |
| Male, \(n\) \%(%) | 26 \(79\)% | 23 \(70\)% | 0.57 |
| Female, \(n\) \%(%) | 7 \(21\)% | 10 \(30\)% | |
| Age, years | 67 \([60–73]\) | 65 \([56–70]\) | 0.17 |
| BMI, kg/m\(^2\) | 27.6 \([25.4–31.1]\) | 27.7 \([24.3–30.7]\) | 0.40 |
| APACHE II | 15 \([13–19]\) | 15 \([10–19]\) | 0.77 |
| Days between COVID-19 symptoms and hospital admission | 7 \([4–10]\) | 7 \([5–11]\) | 0.72 |
| Days between COVID-19 symptoms and ICU admission | 10 \([7–13]\) | 10 \([6–14]\) | 0.96 |
| Day of secondary infection (relative to hospital admission) | 16 \([13–22]\) | NA | |
| Day of secondary infection (relative to ICU admission) | 14 \([9–21]\) | NA | |
| **Medical history, \(n\) \%(%)** | | | |
| Cardiovascular insufficiency | 9 \(27\)% | 9 \(27\)% | 1.00 |
| Hypertension | 17 \(52\)% | 16 \(48\)% | 1.00 |
| Respiratory insufficiency | 2 \(6\)% | 3 \(9\)% | 1.00 |
| Renal insufficiency | 0 \(0\)% | 1 \(3\)% | 1.00 |
| Metastatic neoplasm | 2 \(6\)% | 3 \(9\)% | 1.00 |
| Immunological insufficiency | 0 \(0\)% | 1 \(3\)% | 1.00 |
| COPD | 3 \(9\)% | 3 \(9\)% | 1.00 |
| Diabetes | 11 \(33\)% | 4 \(12\)% | 0.08 |
| Hematologic malignancy | 0 \(0\)% | 1 \(3\)% | 1.00 |

Continuous data are presented as median [interquartile range]. \(p\) values were calculated using Mann-Whitney \(U\) tests (continuous data) and Fisher exact tests (categorical data).

NA not applicable
Fig. 1 (See legend on next page.)
Abbreviations
COVID-19: Coronavirus disease 2019; PCT: Procalcitonin; CRP: C-reactive protein

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Authors’ contributions
MvB, MK, PP, TF, and JS designed the study. PP and JS scored the secondary infection episodes. TF, MK, and PP designed the database/collected the patient-related information. MvB, DW, MK, and PP analyzed and interpreted the data. MvB and JS drafted the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors revised and approved the final manuscript for publication.

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Competing interests
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