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Short Communication

Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit



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1. Introduction

The coronavirus-2019 (COVID-19) pandemic caused by the virus SARS-CoV-2 infection has imposed significant demand on all healthcare systems. Based on national and international guidance which were mostly anecdotal [1], COVID-19 patients admitted to our General Intensive Care Unit (GICU) were routinely commenced on antibiotics to cover possible secondary bacterial lower respiratory tract infection (LRTI). The antibiotics should have been reviewed after 48 h, however, it was challenging to stop early because of the many factors such as persistent hyperinflammatory status, ongoing/worsening lung infiltrates with the need for continued mechanical ventilation, and also partly because of the lack of reliable indicators of bacterial infection.

As a quality improvement project (QIP), procalcitonin (PCT) was introduced in our GICU in April–2020 as an antibiotic stewardship (ABS) tool. Around a month from this the UK's National Institute for Health and Care Excellence (NICE) published a COVID-19 rapid guideline and suggested that there is insufficient evidence to recommend routine PCT testing to guide decisions about antibiotics and encouraged centres already using PCT to participate in research and data collection [2]. Here, we report our findings of the use of PCT in COVID-19 critically ill patients to determine the following:

- The antibiotic usage in COVID-19 patients post introduction of PCT within 7 days of ICU admission.
- If mortality and length of stay in intensive care are affected based on PCT values and antibiotic decision making.

2. Methods

A prospective, single-centre, cohort study involving pragmatic assessment of PCT in COVID-19 patients admitted to GICU at

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University Hospital Southampton NHS Foundation Trust was carried out from 6 April to 22 May, 2020 (our peak).

All patients were tested positive for SARS-CoV-2 using real time polymerase chain reaction (RT-PCR) from combined nose and throat swabs in a VIRO CULT virus transport medium. Samples were extracted and purified using magnetic particle extraction on the Thermo Scientific KingFisher Flex. PCR amplification was performed on the Applied Biosystems (ABI) 7500 using the Viasure SARS-CoV-2 RT-PCR kit, targeting ORF1ab and the N gene. Additionally, primers and probes for the World Health Organization E gene assay (including an internal positive amplification control from extraction) was also used to enhance the sensitivity. All patients were followed up to 30 days, or until they died, to ascertain outcome data.

PCT was measured from serum samples using sequential two-step immunoassay ('sandwich') assay (Beckman Coulter) as part of its access range for the DxI immunoassay instruments (800 version). Proposed antibiotic decisions based on PCT cut-off levels have previously been published in an international consensus guide incorporating PCT values with clinical judgement and experience [3]. A level of 0.5 µg/L was used as the upper limit to help determine the probability of bacterial infection, along with clinical judgement of a bacterial infection.

This was done as a QIP, hence ethical approval was not sought.

3. Results

Fifty-two patients received PCT testing on their admission to GICU, categorised into PCT valve <0.5 µg/L (low PCT group $n = 25$) and PCT value >0.5 µg/L (high PCT group $n = 27$). Comparison of these two groups is summarised in Table 1.

The use of antibiotics within the first 7 days of admission was lower in the low PCT group (5 days) compared with 7 days with high PCT ($P < 0.001$). There was also significant difference in the duration of ICU stay between both groups (5 days vs. 15 days; $P = 0.03$). Furthermore a larger number of patients requiring invasive ventilation in the high PCT group, compared with the low PCT group, and a better survival trend in the low PCT group were noted. These were not statistically significant.

4. Discussion

Although there has been a rapid increase in COVID-19-related publications recently, none are specific to the use of PCT to guide antimicrobial de-escalation in critically unwell patients with COVID-19 pneumonia. A meta-analysis concluded that PCT > 0.5 ng/mL is associated with increased risk of progression to critical illness even particularly when the WBC is initially normal or reduced [4].

Table 1
Demographics, clinical, and outcome data among patients with PCT < 0.5 µg/L vs. those with PCT > 0.5 µg/L.

	PCT < 0.5	PCT > 0.5	P-value when significant
Patient data and demographics			
Number of patients (n)	25	27	
Age (years) ^a	54.4 (± 11.3)	57.9 (± 10.0)	
Male (%)	72	55.6	
Severity of illness and interventions			
Charlson's Comorbidity Index ^b	1 (0–3)	2 (1–3)	
Days symptomatic before admission ^b	10 (6.75–14)	7 (6–11)	
True positive microbiology, n (%) (first 7 days)	2 (8%)	7 (26%)	
Temperature °C, day 1 ^b	37.1 (36.7–37.7)	37.4 (36.6–38.1)	
Temperature °C, average over first week ^b	36.8 (36.4–37.5)	37.1 (36.5–37.7)	<0.001
Median SOFA score points ^b	3 (3–4)	5 (4–7)	<0.001
Median APACHE II score ^b	12 (8–15)	19 (12.5–24.5)	0.012
Ventilation support			
Invasive ventilation no (%)	15 (60%)	21 (77.8%)	
Non-invasive ventilation no (%)	10 (40%)	6 (22.2%)	
Renal replacement (in first 7 days)	0	8	0.0044
Antibiotic therapy in first 7 days ^d (days) ^b	5 (4–5)	7 (7–7)	<0.001
Blood markers			
White cell count (10^9 /L) (first week) ^b	8.7 (6.9–10.7)	9.9 (7.3–14.0)	0.001
White cell count (10^9 /L) (day 1) ^b	9.6 (6.32–11.5)	10.6 (7.08–12)	
CRP (mg/L) (first week) ^b	138 (88.8–202)	232 (156–312)	<0.001
CRP (mg/L) (day 1)	139 (112–182)	174 (126–276)	
Lymphocyte cell count (10^9 /L) (first week) ^b	1.05 (0.8–1.42)	0.8 (0.6–1.37)	<0.001
Lymphocyte cell count (10^9 /L) (day 1) ^b	0.95 (0.7–1.3)	0.9 (0.6–1.28)	
Outcome data			
Alive at day 30 (%)	96	85.2	
Length of ICU stay (days) ^b	5 (3–16)	15 (7–21.75)	0.03
Percentage discharged from hospital at endpoint of study	96%	59%	
Length of hospital stay (days) ^{b,e}	15.5 (11–24.2)	20 (10–23)	

Description data, severity score, and outcome of procalcitonin (PCT) < 0.5 µg/L vs. PCT > 0.5 µg/L.

APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment.

^a Data are presented as mean $\pm$ standard deviation.

^b Data are presented as median and interquartile range.

^c Culture from normally sterile site e.g. blood culture; or pure growth of a significant isolate from bronchoalveolar lavage, or positive legionella or pneumococcal antigen tests or an organism deemed significant by an infection specialist.

^d Compliance with de-escalate or stop antibiotics in the low PCT group was only 56%, i.e. 44% of the time clinicians ignored the low PCT results and carried on antibiotics.

^e Amongst patients discharged from hospital ($n = 24$ [PCT < 0.5] and $n = 16$ [PCT > 0.5]). Data were collected from our intensive care clinical information system (CIS) (Metavision, iMDsoft, Tel Aviv, Israel) and hospital laboratory information system (eQuest, University Hospital Southampton, Southampton, UK). All statistical analysis and data processing were performed using R (R Core Team, Vienna, Austria). Normally distributed data are presented as mean and standard deviation, whereas data suspected to be non-normally distributed were confirmed by a Shapiro–Wilk test. These data are presented as median and IQR. Significance testing of continuous, non-parametric variables was performed using a Mann–Whitney U -test. Categorical variables were examined using Fisher's Exact test. A cut-off of $P < 0.05$ was used throughout.

Limitations of our study include, being conducted in a single centre, a relatively small number of patients, and lack of randomisation. Additionally, the clinicians might have been more inclined to stop antibiotics sooner in the low PCT group as they appeared less unwell; however, in reality these would have continued for 7 days as per GICU protocol.

Despite these, our data suggests that the use of PCT as a guide for de-escalation of antibiotics significantly reduced antibiotic usage by 2 days in COVID-19 patients and can be used as an ABS tool. Larger randomised controlled trials are needed to evaluate this further and to confirm these findings and cost effectiveness.

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