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Brief report

The feasibility of procalcitonin and CPIS score to reduce inappropriate antibiotics use among severe-critically ill COVID-19 pneumonia patients: A pilot study

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Antibiotics have been extensively used in COVID-19 patients without a clear indication. We conducted a study to evaluate the feasibility of procalcitonin along with the "Clinical Pulmonary for Infection Score" (CPIS) as a strategy to reduce inappropriate antibiotic use. Using procalcitonin and CPIS score (PCT-CPIS) successfully reduced inappropriate antibiotics use among severe-critically ill COVID-19 pneumonia patients (45% vs 100%; $P < .01$). Compared to "non PCT-CPIS" group, "PCT-CPIS" group was associated with a reduction in the incidence of multidrug-resistant organisms and invasive fungal infections (18.3% vs 36.7%; $P = .03$), shorter antibiotic duration (2 days vs 7 days; $P < .01$) and length of hospital stay (10 days vs 16 days; $P < .01$).

COVID-19 pneumonia is associated with a mortality up to 20% varying by country[1] with the number of global deaths over 5 million.[2] Antibiotics have been extensively used in COVID-19 patients in intensive care units (ICUs) without a clear indication.[3] According to a previous study, the frequency of bacterial pneumonia in COVID-19 patients was 6.9%, while >70% of patients received antibiotics.[4] This is likely due to the clinical findings of COVID-19 pneumonia overlapping with those of bacterial pneumonia and the lack of reliable indicators of bacterial infection. Strategies that distinguish bacterial from viral pneumonia are desirable. We conducted a study to evaluate the feasibility of procalcitonin (PCT) along with the "Clinical Pulmonary for Infection Score" (CPIS) as a strategy to reduce inappropriate antibiotics use among severe-critically ill COVID-19 pneumonia patients.

METHODS

This prospective cohort study was performed at 2 ICUs for severe-critically ill COVID-19 pneumonia patients at Thammasat University Hospital (TUH) from April 1, 2021 to August 8, 2021. The antibiotic appropriateness was defined based per Kunin et al.[5] (Supplementary 1). The criteria of PCT were modeled from PCT-guided antibiotic stewardship in Asia-Pacific countries.[6] CPIS score for pneumonia was used based on Singh et al.[7] and modified for use in COVID-19 pneumonia patients.[8] COVID-19 pneumonia severity was defined as previously described.[9] The inclusion criteria were adults (≥18 years) with severe-critically ill COVID-19 pneumonia and admitted to an ICU. Patients who received antibiotics <24 hours or for other indications (eg, surgical prophylaxis), were excluded. Upon admission, the researchers calculated the CPIS score (COVID-19 version)[8] and ordered an admission PCT for patients with severe-critically ill COVID-19 pneumonia in both ICUs. If CPIS score <6 and PCT <0.5 μg/L, the researchers notified the treating physicians to consider not initiating antibiotics. On hospitalization day 3, CPIS score and PCT were

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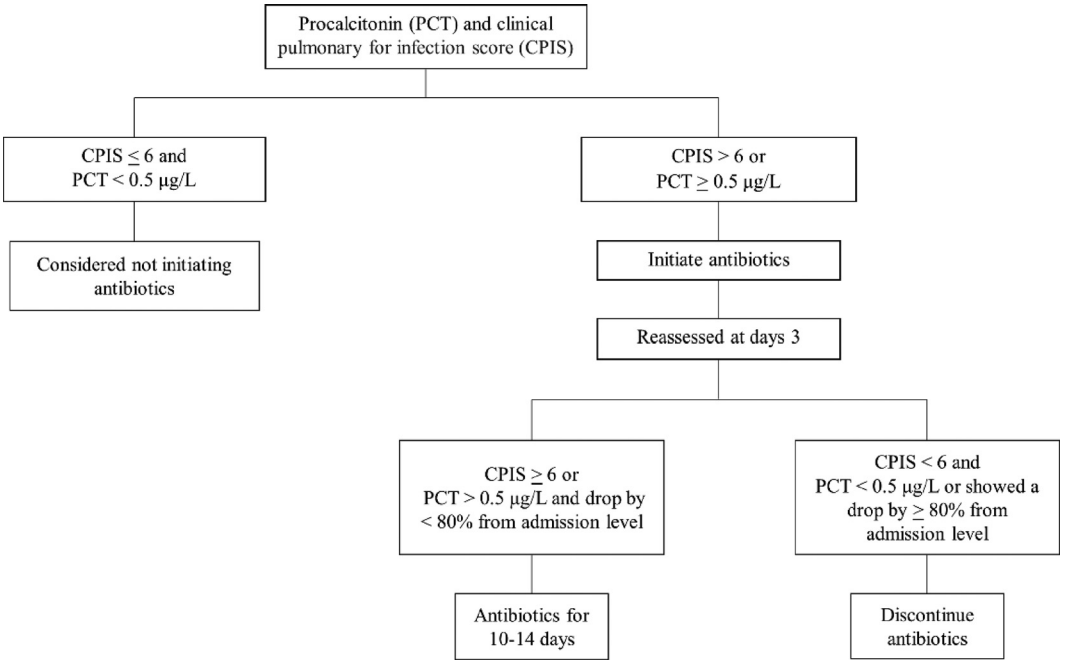

Fig 1. Protocol of procalcitonin and CPIS score.

reassessed. If CPIS <6 and PCT <0.5 μg/L or PCT dropped by ≥80% from the admission level, the researchers re-notified the treating physicians for antibiotics discontinuation (Fig 1). The final decision for antibiotics usage and whether to follow the PCT-CPIS strategy was made by the treating physicians. Cases that physicians followed PCT-CPIS protocol (Fig 1) served as the intervention group while the group that did not follow the protocol (non PCT-CPIS) served as the control group. In these ICUs, routine evaluations of bacterial co-infections at all sites were performed at admission as clinically indicated and during hospitalization if the patients were not responding to therapy by evaluating sputum Gram stain and culture, urine culture, blood cultures and chest x-ray.

The primary goal in this study was to evaluate the feasibility of PCT and CPIS score to reduce inappropriate antibiotics use among severe-critically ill COVID-19 pneumonia patients, by decreasing the rate of inappropriate empirical antibiotics initiation and/or discontinuing antibiotics in 72 hours. The secondary outcomes were antibiotic duration, LOS, 30-day mortality, the prevalence of multidrug-resistant organisms (MDRO) and invasive fungal infection (IFI).

Data collected included demographics, comorbidities, body mass index (BMI), admission PCT level and CPIS score, PCT and CPIS score on hospitalization days 3, COVID-19 pneumonia severity (eg, severe, critically), type of corticosteroids used, antibiotic duration, LOS, 30-days and infectious disease-related mortality, types of MDROs and IFIs. This study was approved by the Institution Review Board.

All analyses were performed using SPSS, version 26 software (IBM, Armonk, NY). Chi-square tests were used to compare categorical variables. Independent t-tests were used for continuous data. All *P* values were 2-tailed, and $P < .05$ was considered statistically significant. A multivariate analysis was used to evaluate factors associated with 30-day mortality. Adjusted odd ratios (aORs) and 95% confidence intervals (CIs) were calculated.

RESULTS

There were 120 patients enrolled in this study; 60 patients were in “PCT-CPIS” group and 60 patients were in “non PCT-CPIS” group. The median age for study participants was 61 years (range, 26-87 years); the most common underlying diseases were hypertension (43.3%) and diabetes mellitus (25.8%). All COVID-19 pneumonia patients were categorized as critically (40.0%) or severely (60.0%) ill. Demographics and baseline characteristics of “PCT-CPIS” versus “non PCT-CPIS” group were compared (Table 1).

The overall inappropriate antibiotic use in this study was 72.5% (87/120), which was comparable to the baseline inappropriate antibiotic use in non-COVID-19 ICU (85%). Compared to “non PCT-CPIS” group, the “PCT-CPIS” group were less likely to have inappropriate antibiotics used (45.0% vs 100%; $P < .01$) inclusive of less inappropriate empirical antibiotic initiation (58.3% vs 100%, $P < .01$) and have more antibiotics discontinued in 72 hours (13.3% vs 0%, $P < .01$). Analysis of CPIS alone (OR = 0.77; 95% CI, 0.69-0.86) or PCT alone (OR = 0.16; 95% CI, 0.05-0.58) suggested that both components significantly reduced inappropriate antibiotic use. The “PCT-CPIS” group had a significantly shorter total antibiotic duration (2 days vs 7 days; $P < .01$) and LOS (10 days vs 16 days; $P < .01$). Notably, there was a significantly lower incidence of MDROs and IFIs in the “PCT-CPIS” group (18.3% vs 36.7%; $P = .03$) and a trend for the lower incidence of MDR-*Acinetobacter baumannii* (11.7% vs 23.3%; $P = .09$). The 30-day mortality and infectious disease-related mortality were not significantly different between the 2 groups.

By multivariate analysis, factors associated with 30-day mortality were coronary artery disease (aOR, 13.66; 95% CI, 1.21-154.51), initial CPIS score ≥6 (aOR, 5.46; 95% CI, 1.15-25.96), admission PCT level ≥0.5 μg/L (aOR, 6.60; 95% CI, 1.94-22.44), use of methylprednisolone pulses (aOR, 3.44; 95% CI, 1.11-10.64) and occurrence of MDRO and/or IFI (aOR, 18.36; 95% CI, 5.45-61.88). The only factor associated with a reduction in inappropriate antibiotic use were CPIS score ≤6 *and* admission PCT level <0.5 μg/L (aOR, 0.25; 95% CI, 0.07-0.93).

DISCUSSION

There are several notable findings in our study. First, PCT-CPIS was implemented successfully to reduce inappropriate antibiotics use

Table 1
Demographics and baseline characteristics of study populations compared "PCT-CPIS" group versus "non PCT-CPIS" group

Variable	Total (%) (N = 120)	PCT-CPIS group (%) (N = 60)	Non PCT-CPIS group (%) (N = 60)	*P*-value
Age, median year (range)	61 (26-87)	61 (28-81)	61 (26-87)	.98
Sex, male	66 (55.0)	35 (58.3)	31 (51.7)	.46
BMI (kg/m^2), median (range)	26.3 (18.7-60.6)	26.3 (19.0-60.6)	26.4 (18.7-53.3)	.76
Underlying diseases				
None	40 (33.3)	18 (30.0)	22 (36.7)	.44
Diabetes mellitus	31 (25.8)	16 (26.7)	15 (25.0)	.84
Hypertension	52 (43.3)	25 (41.7)	27 (45.0)	.71
Dyslipidemia	30 (25.0)	14 (23.3)	16 (26.7)	.67
Chronic kidney disease	10 (8.3)	7 (11.7)	3 (5.0)	.19
Coronary artery disease	6 (5.0)	2 (3.3)	4 (6.7)	.40
Atrial fibrillation	2 (1.7)	1 (1.7)	1 (1.7)	1.00
Asthma	4 (3.3)	4 (6.7)	0 (0)	.04
COVID-19 severity*				
Critically	48 (40.0)	22 (36.7)	26 (43.3)	.37
Median APACHE II score (range)	15 (8-30)	14 (8-25)	15 (8-30)	.75
Median CPIS score (range)				
Admission	4 (2-9)	4 (2-9)	4 (2-8)	.10
On hospitalization d 3	5 (2-9)	5 (2-9)	5 (2-8)	.10
Median procalcitonin level (μg/L) (range)				
Admission	0.18 (0.03-23.3)	0.31 (0.03-23.3)	0.15 (0.03-6.5)	.33
On hospitalization d 3	0.10 (0.04-34.9)	0.10 (0.04-34.9)	0.13 (0.04-6.0)	.10
Outcomes				
Primary outcome				
Inappropriate ATB use	87 (72.5)	27 (45.0)	60 (100.0)	<.01
Inappropriate empirical ATB initiation	95 (79.2)	35 (58.3)	60 (100.0)	<.01
Discontinuation of ATB in 72 h	8 (6.7)	8 (13.3)	0 (0.0)	<.01
Secondary outcome				
ATB duration, median (range)	7 (0-24)	2 (0-17)	7 (4-24)	<.01
Length of hospital stay, median (range)	12 (3-50)	10 (3-50)	16 (3-47)	<.01
MDRO and IFI	33 (27.5)	11 (18.3)	22 (36.7)	.03
MDR-*Acinetobactor baumannii*	21 (17.5)	7 (11.7)	14 (23.3)	.09
MDR-*Pseudomonas aeruginosa*	2 (1.7)	2 (3.3)	0 (0.0)	.15
ESBL-*Klebsiella pneumoniae*	3 (2.5)	1 (1.7)	2 (3.3)	.56
ESBL-*Escherichia* coli	2 (1.7)	0 (0)	2 (3.3)	.15
Invasive fungal infection	5 (4.2)	1 (1.7)	4 (6.7)	.17
30-d mortality	41 (31.2)	20 (33.3)	21 (35.0)	.85
Infection disease related mortality	30 (25.0)	12 (20.0)	18 (30)	.21
Severe ARDS	8 (6.7)	6 (10.0)	2 (3.3)	.14
Others†	3 (2.5)	2 (3.3)	1 (1.7)	.56

Note. *ARDS*, acute respiratory distress syndrome *ATB*, antibiotics; *BMI*, body mass index; ESBL, extended spectrum beta-lactamase; *ICU*, intensive care unit; *IFI*, invasive fungal infection; *MDRO*, multidrug-resistant organisms.
*COVID-19 severity was defined based on Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia[8] which critically cases meeting any of the following criteria including respiratory failure and requiring mechanical ventilation, shock, or with other organ failure that requires ICU care.
†Upper gastrointestinal bleeding, acute pulmonary embolism.

among severe-critically ill COVID-19 pneumonia patients. Second, PCT-CPIS led to significant reductions in MDROs and IFIs incidences. Furthermore, this strategy decreased antibiotic duration and shortened LOS. To our knowledge, this is the first study of PCT-CPIS to reduce inappropriate antibiotics use among severe-critically ill COVID-19 pneumonia patients.

Studies reported that <10% of COVID-19 pneumonia patients experience bacterial co-infection during hospital admission, while antibiotics use occurs in up to 70% of patients.[4,10] While the National Institute for Health and Care Excellence (NICE)[11] does not currently recommend routine PCT testing to guide decisions about antibiotic use and using PCT in COPD may increase mortality,[12] the American Thoracic Society and Infectious Diseases Society of America have suggested that procalcitonin could be helpful in limiting overuse of antibiotics in patients with COVID-19 pneumonia.[13] Our findings support the role of PCT in combination with CPIS score to help guide for initiation and discontinuation of antibiotics in severe-critically ill COVID-19 pneumonia patients in ICUs. Interestingly, we found that the high level of procalcitonin ≥0.5 μg/L together with an initial CPIS score 6 was associated with 30-day mortality. This suggests that these measures could be used as independent factors to predict mortality in critically ill COVID-19 patients. However, the adherence to PCT-CPIS protocol was less than optimal, thus additional studies are needed to identify strategies to improve adherence and acceptability of PCT-CPIS protocol.

There are some limitations in this study. First, the small sample size in this study limited our capacity to detect significant reductions in certain outcomes (eg, 30-day mortality). Second, this study was performed in single-center among ICU patients that may limit generalization. Third, the fact that this study was not a randomized controlled trial and selecting "PCT-CPIS" to compare with "non PCT-CPIS" group, potential unmeasured confounders and biases may have impacted our findings.

In conclusion, PCT-CPIS can be implemented successfully to reduce inappropriate antibiotic use in severe-critically ill COVID-19 pneumonia patients in an ICU. Our data suggested that the use of PCT along with CPIS score to guide decisions on antibiotics use among COVID-19 pneumonia patients associated with many benefits. Additional randomized controlled multi-center studies to evaluate the role of PCT and/or CPIS to reduce inappropriate antibiotics use are needed.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2022.01.030.

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