Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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

Ornnicha Sathitakorn MD a, Kittiya Jantarataneewat PharmD b,c,d, David J. Weber MD, MPH e, David K. Warren MD, MPH f, Sira Nanthapisal MD, PhD c,d,g, Sasinuch Rutjanawech MD a,c,d, Piyaporn Apisarnthanarak MD h, Anucha Apisarnthanarak MD a,c,d,*

Division of Infectious Diseases, Faculty of Medicine, Thammasat University, Prathum Thani, Thailand
Department of Pharmaceutical care, Faculty of Pharmacy, Thammasat University, Prathum Thani, Thailand
Division of Infectious Diseases, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
Division of Infectious Diseases, Washington University School of Medicine, St. Louis, MO, USA
Division of Pediatrics, Faculty of Medicine, Thammasat University, Prathum Thani, Thailand
Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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 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).

© 2022 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

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. (Supplementary 1). The criteria of PCT were modeled from PCT-guided antibiotic stewardship in Asia-Pacific countries. CPIS score for pneumonia was used based on Singh et al. and modified for use in COVID-19 pneumonia patients. COVID-19 pneumonia severity was defined as previously described. 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) 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
RESULTS

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 < 0.01) inclusive of less inappropriate empirical antibiotic initiation (58.3% vs 100%, P < 0.01) and have more antibiotics discontinued in 72 hours (13.3% vs 0%, P < 0.01). 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 was 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.
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.\(^{10}\) 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 \(>0.5 \mu g/L\) 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 of 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 antibiotic 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.
References

1. World Health Organization. Estimating Mortality From COVID-19. 2020. Accessed September 18, 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.

2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report. 2021. Accessed November 23, 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.

3. Heesom L, Rehnberg L, Nasim-Mohi M, et al. Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit. J Glob Antimicrob Resist. 2020;22:782–784.

4. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26:1622–1629.

5. Kunin CM, Tupasi T, Craig WA. Use of antibiotics: a brief exposition of the problem and some tentative solutions. Ann Intern Med. 1973;79:555–560.

6. Lee CC, Kwa ALH, Apisarnthanarak A, et al. Procalcitonin (PCT)-guided antibiotic stewardship in Asia-Pacific countries: adaptation based on an expert consensus meeting. Clin Chem Lab Med. 2020;58:1983–1991.

7. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med. 2000;162:505–511.

8. Schurink CAM. Clinical Pulmonary Infection Score (CPS) for Ventilator-Associated Pneumonia (VAP). 2020. Accessed September 18, 2021. https://www.mdcalc.com/clinical-pulmonary-infection-score-cps-ventilator-associated-pneumonia-vap.

9. Wei PF. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). Chin Med J (Engl). 2020;133:1087–1095.

10. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020;71:2459–2468.

11. National Institute for Health and Care Excellence (NICE). COVID-19 Rapid Guideline: Identifying Secondary Bacterial Pneumonia. 2021. Accessed November 25, 2021. https://www.nice.org.uk/guidance/NG178.

12. Daubin C, Valette X, Thollière F, et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. Intensive Care Med. 2018;44:428–437.

13. Metlay JP, Waterer GW. Treatment of community-acquired pneumonia during the coronavirus disease 2019 (COVID-19) pandemic. Ann Intern Med. 2020;173:304–305.