Letter to the Editor

A call for antimicrobial stewardship in patients with COVID-19: a nationwide cohort study in Korea

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To the Editor

The overuse of antibiotics for coronavirus disease 2019 (COVID-19) poses a threat [1]. Less than 8% of patients with COVID-19 have respiratory bacterial co-infections [2], and the current U.S. National Institutes of Health (NIH) guidelines do not recommend antibiotic prescription for patients with COVID-19 unless there is clinical suspicion of bacterial infection [3]. We reviewed the large nationwide insurance claims database of the Health Insurance Review and Assessment Service of Korea (HIRA) to identify the antibiotic prescription frequency for patients with COVID-19. As the HIRA is the only health insurance policy in Korea and is responsible for all hospitalization-related costs of COVID-19 patients, complete antibiotic claims data for the country could be evaluated. We retrospectively reviewed data on all adults (age ≥19 years) with confirmed COVID-19 admitted to hospitals or living treatment centres between 1st January and 15th May 2020. (Living treatment

centres are non-hospital facilities where patients with mild COVID-19 can be admitted [4].)

Antibiotic use was quantified by days of therapy (DOTs) per 1000 patient-days. Antibiotics were classified into two groups: one group that covered either methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* (anti-MRSA or anti-pseudomonal), and the other antibiotic group. Anti-MRSA or anti-pseudomonal antibiotics, such as glycopeptides, oxazolidinones, piperacillin–tazobactam, carbapenems, polymyxins, cefepime, ceftazidime, or monobactams were mainly used for hospital-acquired pneumonia rather than community-acquired infection [5]. Fluoroquinolones were included in the other group because they were recommended as monotherapy for community-acquired pneumonia.

COVID-19 severity was classified as mild to moderate or severe to critical, according to the NIH guidelines [3]. Patients with a requirement for low-flow oxygen therapy (i.e., nasal cannula), high-flow oxygen therapy (i.e., high-flow nasal cannula or mechanical ventilation), inotropic drugs, or extracorporeal membrane oxygenation were classified as having severe to critical disease. Patients hospitalized for influenza from a national health insurance service sample cohort of 1 000 000 patients admitted in Korea between 2002 and 2015 were reviewed. Patients with influenza were analysed based on the same severity classification and compared to patients with COVID-19. The study was approved by the Seoul National University Bundang Hospital Institutional Review Board (No. X-2008-633-902).

During the study period, of 6871 patients with COVID-19, 2419 (35.21%) and 536 (7.80%) were prescribed total antibiotics and anti-MRSA or anti-pseudomonal antibiotics, respectively (Table 1). Overall, 5928 patients (86.28%) and 943 patients (13.72%) had mild to moderate and severe to critical disease, respectively, and 27.99% and 80.59% of these patients were prescribed antibiotics (Supplementary Table S1). Additionally, 2640 patients (38.42%) were prescribed lopinavir/ritonavir and 2082 (30.30%) hydroxychloroquine/chloroquine.

The total antibiotic use and anti-MRSA or anti-pseudomonal antibiotic use were 364.32 and 71.99 DOTs/1000 patient-days,

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Table 1
Clinical characteristics of patients with coronavirus disease 2019 (COVID-19) and antibiotic use

	Total (n = 6871)	Anti-MRSA or anti-pseudomonal antibiotics[a] (n = 536)	Other antibiotics (n = 1883)	No antibiotic use (n = 4452)	p[b]
Age, mean (±SD) (years)	47.34 (±19.01)	67.94 (±14.45)	54.77 (±17.55)	41.72 (±17.22)	<0.01
Age group					<0.01
19–64 years	5562 (80.95)	218 (40.67)	1317 (69.94)	4027 (90.45)	
≥65 years	1309 (19.05)	318 (59.33)	566 (30.06)	425 (9.55)	
Sex, male	2773 (40.36)	263 (49.07)	714 (37.92)	1796 (40.34)	<0.01
Comorbidities					
Diabetes mellitus	1114 (16.21)	203 (37.87)	421 (22.36)	490 (11.01)	<0.01
Cardiovascular disease	589 (8.57)	136 (25.37)	221 (11.74)	232 (5.21)	<0.01
Chronic respiratory disease	1837 (26.74)	209 (38.99)	634 (33.67)	994 (22.33)	<0.01
Renal disease	215 (3.13)	46 (8.58)	67 (3.56)	102 (2.29)	<0.01
Chronic liver disease	856 (12.46)	116 (21.64)	298 (15.83)	442 (9.93)	<0.01
Peptic ulcer disease	1040 (15.14)	141 (26.31)	354 (18.80)	545 (12.24)	<0.01
Chronic neurological disease	691 (10.06)	184 (34.33)	240 (12.75)	267 (6.00)	<0.01
Malignancy	306 (4.45)	53 (9.89)	110 (5.84)	143 (3.21)	<0.01
Musculoskeletal and rheumatological disease	211 (3.07)	27 (5.04)	72 (3.82)	112 (2.52)	<0.01
Immune deficiency and HIV infection	3 (0.04)	1 (0.19)	0 (0.0)	2 (0.04)	0.19
Charlson comorbidity index, median (IQR)	1 (0–2)	2 (1–4)	1 (0–3)	0 (0–1)	<0.01
Disease severity of COVID-19					<0.01
Mild to moderate	5928 (86.28)	131 (24.44)	1528 (81.15)	4269 (95.89)	
Severe to critical	943 (13.72)	405 (75.56)	355 (18.85)	183 (4.11)	
Lopinavir/ritonavir	2640 (38.42)	426 (79.48)	1336 (70.95)	878 (19.72)	<0.01
Hydroxychloroquine/chloroquine	2082 (30.30)	369 (68.84)	1023 (54.33)	690 (15.50)	<0.01

MRSA, methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.
[a] Activity against either MRSA (such as glycopeptides and oxazolidinones) or *Pseudomonas aeruginosa* (such as piperacillin–tazobactam, carbapenems, polymyxins, cefepime, ceftazidime, and monobactams) were included, but fluoroquinolones were excluded because they are recommended as part of monotherapy for community-acquired pneumonia.
[b] Analysis of variance was used to compare anti-MRSA or anti-pseudomonal antibiotics, other antibiotics, and no antibiotic use groups.

respectively (Supplementary Table S1). The most commonly used antibiotics were fluoroquinolones (144.07 DOTs/1000 patient-days), third-generation cephalosporins (84.55 DOTs/1000 patient-days), and macrolides (46.16 DOTs/1000 patient-days). In patients with severe to critical COVID-19, total antibiotic use was 1295.27 DOTs/1000 patient-days. Anti-MRSA or anti-pseudomonal antibiotics were prescribed more frequently in patients with severe to critical COVID-19 (451.15 DOTs/1000 patient-days) than in those with mild to moderate disease (11.68 DOTs/1000 patient-days, $p < 0.01$).

When compared to patients hospitalized for influenza in the past, patients with influenza were older (COVID-19 versus influenza, mean 47.34 versus 54.32, $p < 0.01$, Supplementary Table S2), had a higher Charlson comorbidity index (1.25 versus 1.36, $p < 0.01$), and more antibiotics were prescribed (35.20% versus 72.52%, $p < 0.01$). However, more anti-MRSA or anti-pseudomonal antibiotics were prescribed to patients with COVID-19 in the severe to critical group (DOTs/1000 patient-days 451.15 versus 243.54, $p < 0.01$), probably because of concerns about the novel infectious disease.

Multivariable logistic regression identified older age (adjusted odds ratio (aOR) 1.05, 95% confidence interval (95%CI) 1.04–1.06, $p < 0.01$, Supplementary Table S3), male sex (aOR 1.36, 95%CI 1.03–1.80, p 0.03), and chronic neurological disease (which included cerebrovascular disease, dementia, hemiplegia, etc.) (aOR 1.45, 95%CI 1.04–2.04, p 0.03) to be independently associated with anti-MRSA or anti-pseudomonal antibiotic use. Moreover, a similar trend was observed with severe to critical COVID-19 (aOR 14.60, 95%CI 10.88–19.58, $p < 0.01$), use of lopinavir/ritonavir (aOR 4.82,

95%CI 3.61–6.45, $p < 0.01$), and use of hydroxychloroquine/chloroquine (aOR 4.60, 95%CI 3.48–6.07, $p < 0.01$).

A 1:3 propensity score matching analysis performed with age, sex, and COVID-19 severity showed that severe to critical COVID-19 ($p < 0.01$, Supplementary Table S4), use of lopinavir/ritonavir ($p < 0.01$), and use of hydroxychloroquine/chloroquine ($p < 0.01$) were independently associated with anti-MRSA or anti-pseudomonal antibiotic use.

Overall, 42.95% of those with severe to critical COVID-19 were prescribed anti-MRSA or anti-pseudomonal antibiotics. The overuse of these antibiotics for pneumonia to treat potentially drug-resistant bacteria may lead to higher rates of acute kidney injury, *Clostridium difficile* infection, and colonization by multidrug-resistant *P. aeruginosa* and *Acinetobacter baumannii* [5,6]. In order to reduce such collateral damage, antibiotic treatment can be deferred until cultures confirm bacterial superinfection. Even if empirical antibiotic therapy is initiated in patients with severe to critical COVID-19, it should be re-evaluated by appropriate culture tests and stopped as soon as possible if the probability of bacterial coinfection is low [1,7].

A limitation of our study is that since microbiological test results were not reviewed in the HIRA database, the incidence of bacterial coinfection could not be determined. Moreover, it was impossible to distinguish between empirical antibiotic use and targeted antibiotic use for confirmed bacterial coinfection. In addition, the use of antibiotic combination therapy could not be determined from the data.

In conclusion, the rate of antibiotic use in Korea was high in patients with COVID-19, and anti-MRSA or anti-pseudomonal

antibiotics were frequently prescribed for severe to critical patients. As the COVID-19 pandemic continues, there is a need for antimicrobial stewardship to prevent collateral damage related to the overuse of antibiotics.

Author contributions

DHS and MK contributed equally to this work. JJ and ESK conceived and designed the study and had full access to all data. DHS, MK, JJ, and ESK collected and analysed the data. DHS and MK wrote the first draft of the manuscript. DHS, MK, KHS, JJ, ESK, and HBK participated in subsequent revisions.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.10.024.

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