Concise Communication

Antimicrobial stewardship in patients with confirmed coronavirus disease 2019 (COVID-19)

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Abstract
Hospitalized coronavirus disease 2019 (COVID-19) patients receiving antibiotics (n = 173) were retrospectively assigned to the early or late discontinuation groups. The length of therapy was shorter in the early discontinuation group (3 vs 7 days; P = .0001). Mortality rates (14.3% vs 20.7%; P = .316) and length of stay (7 vs 9 days; P = .063) were similar.

Methods
This retrospective cohort study of patients hospitalized with COVID-19 who received respiratory antibiotics during admission was conducted between June 1, 2020, and July 31, 2020. The study was conducted at Norton Healthcare, a community healthcare system in Louisville, Kentucky, with 1,500 licensed beds and 4 adult hospitals. The study was approved by the University of Louisville Institutional Review Board. Inclusion and exclusion criteria can be found in Figure 1.

Date of COVID-19 diagnosis was defined as the date the positive test result populated in the electronic medical record. If the patient was diagnosed with COVID-19 prior to admission, the date reported in the history and physical was used. If neither was available, the admission date was used. The target window was defined as 48 hours before and after the date of COVID-19 diagnosis. Antibiotic length of therapy included the active course at the time of COVID-19 diagnosis. Antibiotics started or restarted later in the admission were not counted toward overall length of antibiotic therapy. Data from AMS interventions to discontinue antibiotics during the target window were collected. Additionally, culture data for urinary, respiratory, blood and cerebrospinal fluid (CSF) samples were collected if samples were obtained within 48 hours of COVID-19 testing. Blood cultures with coagulase-negative Staphylococcus spp in a single set were considered contaminants and were excluded. The first procalcitonin value of admission was collected if available. Lastly, the quick sequential organ-failure assessment (qSOFA) score was collected from the day of COVID-19 diagnosis.

AMS recommendations to discontinue all antibiotics in COVID-19 patients without evidence of bacterial coinfection were made by trained clinical pharmacists. At our institution, dedicated AMS pharmacists independently review patients on antimicrobials and provide recommendations to the primary treatment team.

Results
Overall, 226 patients were screened for inclusion. Among them, 53 patients were excluded, yielding a total sample of 173 patients...
In total, 91 patients (52.6%) met criteria for the early antibiotic discontinuation group and 82 patients (47.4%) were in the late discontinuation group. Groups were similar regarding most characteristics (Table 1). Patients in the late antibiotic discontinuation group were more likely have a fever ($P = .007$) and a first procalcitonin value $>0.5$ ng/mL ($P < .001$). In the early discontinuation group, median recorded antimicrobial length of therapy was 3 days versus 7 days in the late discontinuation group ($P < .001$).

### Table 1. Baseline Characteristics and Severity of Illness

| Characteristic                        | Early Antibiotic Discontinuation ($n = 91$) | Late Antibiotic Discontinuation ($n = 82$) | $P$ Value |
|---------------------------------------|--------------------------------------------|------------------------------------------|-----------|
| Age, median y (IQR)                  | 63 (50,75)                                 | 64 (50,75)                               | .291      |
| Admitted to ICU on admission, no. (%) | 25 (27.5)                                  | 34 (41.5)                                | .056      |
| Admitted to ICU at time of COVID diagnosis | 13/25 (52%)                              | 15/34 (44.1%)                           | .685      |
| ICU length of stay, median d (IQR)   | 7 (4.12)                                   | 7 (3.18)                                 | .402      |
| Required O2, no. (%)                 | 57 (62.6)                                  | 58 (70.7)                                | .333      |
| Required ventilator, no. (%)         | 6 (6.6)                                    | 13 (15.5)                                | .086      |
| Fever $>38^\circ$C, no. (%)          | 25 (27.5)                                  | 39 (47.6)                                | .007      |
| Vasopressors, no. (%)                | 6 (6.6)                                    | 6 (7.3)                                  | 1.000     |
| Any positive culture, no. (%)        | 12 (13.2)                                  | 15 (18.3)                                | .405      |
| Positive urine culture, no. (%)      | 11 (12.1)                                  | 12 (14.6)                                | .659      |
| Positive respiratory culture, no. (%)| 1 (1.1)                                    | 0 (0)                                    | 1.000     |
| Positive blood culture, no. (%)      | 2 (4.4)                                    | 2 (7.3)                                  | .354      |
| Positive CSF culture, no. (%)        | 0 (0)                                      | 0 (0)                                    | NA        |
| qSOFA score                          | 1 (0.1)                                    | 1 (0, 1)                                 | 0.316     |
| First PCT $>0.5$ ng/mL               | n = 6/87 (6.9%)                            | n = 31/80 (38.8%)                        | $<0.001$  |

Note. CSF, cerebrospinal fluid; FiO2, fraction inspired oxygen; ICU, intensive care unit; IQR, interquartile range; O2, oxygen; PaO2, partial pressure oxygen; qSOFA, quick sequential organ-failure assessment; PCT, procalcitonin; NA, not applicable. Growth from a positive respiratory culture: *Serratia marcescens*. Growth from positive blood cultures: *Escherichia coli* ($n = 2$), *Klebsiella pneumoniae* ($n = 1$), and *Staphylococcus capitis* ($n = 1$).

Overall, 62 patients (35.8%) had a documented AMS recommendation with an acceptance rate of 74.2% ($n = 46$). Among patients for whom antibiotics were discontinued early, 38 (41.8%) had an AMS intervention, with an 86.8% acceptance rate. In the group for whom antibiotics were discontinued later, 24 (29.3%) had an AMS intervention, with a 54.2% acceptance rate. There was no significant difference in the prevalence of

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In Fig. 1, 226 patients were screened. Of these, 53 were excluded. 91 patients were in the early discontinuation group and 82 were in the late discontinuation group. Exclusion criteria include age ≥18 years, confirmed COVID-19 defined as positive nasal, nasopharyngeal, or sputum SARS-CoV-2 RT-PCR or serum IgM antibody test approved by the FDA for emergency use authorization, receipt of respiratory antibiotics at time of COVID-19 diagnosis defined as systemic antibiotics with an indication for respiratory tract infection, acute exacerbation of COPD, pneumonia or empiric therapy.

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Exclusion criteria: absolute neutrophil count $<500\ 10^9$ cells/ul, receipt of antibiotics prophylaxis prior to admission, cystic fibrosis, death within 24 hours of admission or COVID-19 diagnosis.
recommendations to stop antibiotics between groups (P = .112), but was a significant difference in acceptance rates (P = .003).

Mortality and length of stay

The overall in-hospital mortality rate was 17.3%. In the early discontinuation group, 13 (14.3%) died, and in the late discontinuation group, 17 (20.7%) died (P = .316). The median lengths of stay were similar between the early and late discontinuation groups at 7 and 9 days, respectively (P = .063). For patients admitted to the intensive care unit (ICU), the median ICU lengths of stay were similar between these groups: 7 days versus 7 days (P = .402).

Discussion

We found no difference in mortality or length of stay between the early and late antibiotic discontinuation groups, suggesting that early discontinuation of antibiotics for respiratory tract infections in COVID-19 may be safe. Vaughn et al. reported that early discontinuation of antibiotics for respiratory tract infections in COVID-19 patients had an AMS recommendation. This finding may change risk of bacterial coinfection or provider risk assessment.7 AMS recommendations could be a key factor in promoting appropriate antibiotic use in COVID-19 patients.

Interestingly, admission to ICU at time to diagnosis, oxygen requirement, vasopressor requirement, and qSOFA score were not major drivers in the decision to discontinue antibiotics. Fever and procalcitonin value >0.5 ng/mL were more common in the late antibiotic discontinuation group, which may have influenced both appropriateness to make recommendations and provider willingness to accept. A single-center retrospective cohort study found that utilizing procalcitonin guidance shortened antibiotic length of therapy in critically ill COVID-19 from 7 days to 5 days (P < .001).5 Our findings also suggest that procalcitonin may be a useful tool to AMS programs.

A survey of physicians found that the majority of respondents believed COVID-19 patients needed a mean 7.12 days of antibiotics, suggesting an assumption of bacterial coinfection, despite evidence that this is not common.6 AMS efforts could be a key influence in challenging this notion. In our cohort, 35.8% of all COVID-19 patients had an AMS recommendation. This finding highlights the need for all prescribers to critically evaluate whether antibiotics are necessary in COVID-19 patients.

The strengths of this study include its description of AMS efforts and outcomes in COVID-19 patients at the point of diagnosis. Within this cohort, there appeared to be no worse outcomes in patients whose antibiotics were discontinued early versus not; however, this study was not powered to detect a mortality difference. Nevertheless, these findings may add to prescriber confidence when discontinuing antibiotics in confirmed COVID-19 patients. Our findings also demonstrate that AMS recommendations may lead to shorter lengths of therapy in COVID-19 patients.

Future studies should describe AMS efforts stratified by severity of illness; this factor did not appear to be predictive of antibiotic decision making in our study. The utility of procalcitonin and other biomarkers to guide AMS efforts in this patient population could warrant larger-scale investigations. The study period occurred prior to spread of SARS-CoV-2 variants and it remains relatively unknown whether infection due to these mutated strains may change risk of bacterial coinfection or provider risk assessment.7 AMS recommendations could be a key factor in promoting appropriate antibiotic use in COVID-19 patients.

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