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Antibiotic Consumption and Stewardship at a Hospital outside of an Early Coronavirus Disease 2019 Epicenter

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ABSTRACT There are scant data on the impact of coronavirus disease 2019 (COVID-19) on hospital antibiotic consumption, and no data from outside epicenters. At our nonepicenter hospital, antibiotic days of therapy (DOT) and bed days of care (BDOC) were reduced by 151.5/month and 285/month, respectively, for March to June 2020 compared to 2018–2019 ($P = 0.001$ and $P < 0.001$). DOT per 1,000 BDOC was increased (8.1/month; $P = 0.001$). COVID-19 will impact antibiotic consumption, stewardship, and resistance in ways that will likely differ temporally and by region.

KEYWORDS COVID-19, SARS-CoV-2, antibiotics, antimicrobial stewardship

The impact of coronavirus disease 2019 (COVID-19) on the volume of antibiotic usage and stewardship practice is unclear (1). In a rapid review and meta-analysis of studies through mid-April 2020, bacterial infections were reported in 7% and 8% of hospitalized patients and critically ill hospitalized patients with COVID-19, respectively (2). Antibiotics were administered to about 70% of hospitalized COVID-19 patients, including 80% to 100% of those in intensive care units (ICUs) (1, 2). The data suggest that COVID-19 might fuel antibiotic overuse. At the same time, it is possible that widespread antibiotic use among patients with COVID-19 has been offset by suspensions of nonessential medical services and reduced overall utilization of health care services. Thus far, data on national and individual hospital antibiotic consumption during the COVID-19 pandemic are sparse. Estimated total prescription fills for amoxicillin and azithromycin, the most commonly prescribed antibiotics in the United States, were each down nationally by >60% for 19 to 25 April 2020 compared with the same week in 2019 (3). Studies from March and April 2020 at an adult and a pediatric hospital in Barcelona, a major European COVID-19 epicenter, reported increased antibiotic days of therapy (DOT) per patient day (4, 5). At a hospital in Richmond, an epicenter within Virginia, DOT per patient day was increased for ceftriaxone and azithromycin in at least some units in April 2020 (6). These studies did not present data on overall hospital antibiotic consumption (i.e., DOT data that were not normalized to patient days). However, volume was likely increased significantly in ICUs of the adult hospital in Barcelona as bed capacity surged by >300% (4). ICU and non-ICU stays were decreased in the pediatric hospital (5). Thus far, there are no data on antibiotic consumption in hospitals outside of a COVID-19 epicenter.

Our objective was to determine the volumes of antibiotic use and stewardship practices at VA Pittsburgh (VAPHS) after COVID-19 restrictions were introduced but before the disease was widespread in the region. We extracted data on antibiotic utilization and patient bed days of care (BDOC) at VAPHS from the VA Corporate Data
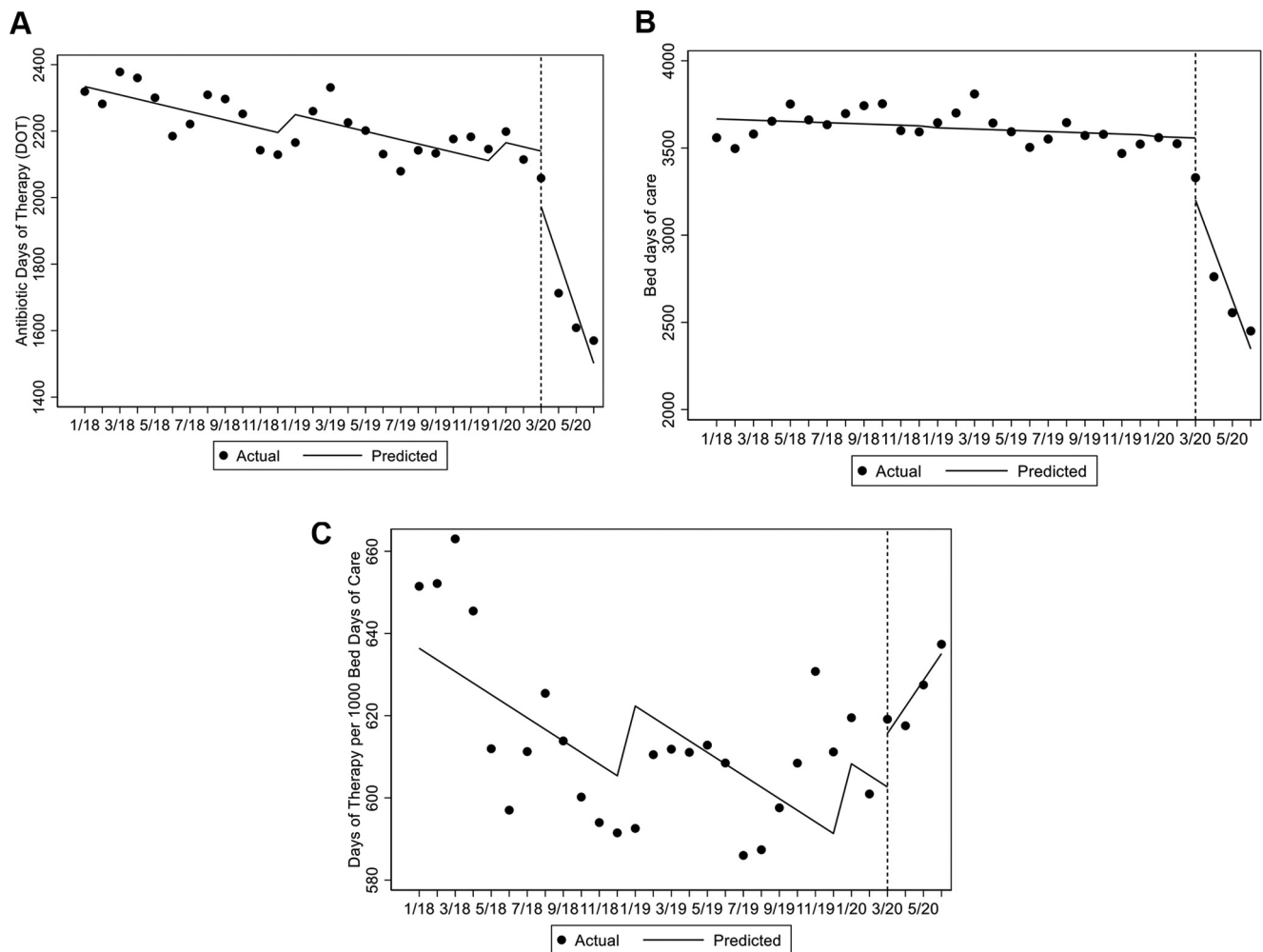
FIG 1 Monthly in-hospital antibiotic use and bed days of care, January 2018 through June 2020. Data are presented as 3-month rolling averages of numbers of in-hospital antibiotic days of therapy (DOT), bed days of care (BDOC), and DOT per 1,000 BDOC (y axis) each month (x axis). Panels A to C show interrupted time series analyses, adjusted for month for DOT, BDOC, and DOT per 1,000 BDOC, respectively. In-hospital antibiotic DOT and BDOC in March to June 2020 were significantly reduced from those in previous months ($P = 0.001$ and $P < 0.001$, respectively). There was an increase in DOT per 1,000 BDOC in March to June 2020 compared to previous months ($P = 0.001$). Antibiotics included any dispensed oral or intravenous formulation of penicillins, cephalosporins, carbapenems, monobactam, fluoroquinolones, macrolides, aminoglycosides, tetracyclines, daptomycin, linezolid, trimethoprim-sulfamethoxazole, vancomycin, clindamycin, nitrofurantoin, metronidazole, and fosfomycin. Non-antipseudomonal penicillins were defined as penicillin, amoxicillin, amoxicillin-clavulanate, oxacillin, nafcillin, and ampicillin-sulbactam. Non-antipseudomonal cephalosporins were defined as cefazolin, cephalexin, cefadroxil, cefuroxime, cefoxitin, ceftriaxone, and cefdinir. Antipseudomonal penicillins were defined as piperacillin-tazobactam and aztreonam. Antipseudomonal cephalosporins were defined as ceftazidime, cefepime, ceftolozane-tazobactam, and ceftazidime-avibactam. Anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) agents were defined as vancomycin, daptomycin, linezolid, and ceftaroline.

Warehouse (Dallas, TX) for November 2017 through June 2020 (monthly data) and 16 February 2020 through 4 July 2020 (weekly data). Aggregated data were expressed as DOT and DOT per 1,000 BDOC, using 3-month and 3-week rolling averages. Antibiotics included in analyses and definitions of groups of antibiotics are presented in the legend to Fig. 1. DOT, BDOC, and DOT per 1,000 BDOC for March to June 2020 were compared to data from the two previous years (beginning January 2018) by interrupted time series regression analysis, with monthly adjustments. Weekly comparisons of DOT, BDOC, and DOT per 1,000 BDOC were made for 1 March through 4 July 2020 using a regression model with monthly correlations for seasonal adjustment.

Key COVID-19-related dates and events for Allegheny County, Pennsylvania (including Pittsburgh), and VAPHS during the study period are presented in Table S1 in the supplemental material. During March to June 2020, there was a monthly adjusted average decrease of 151.5 antibiotic DOT per month compared with January 2018 through February 2020 (6.5% monthly reduction [95% confidence interval {CI}, 3.0% to
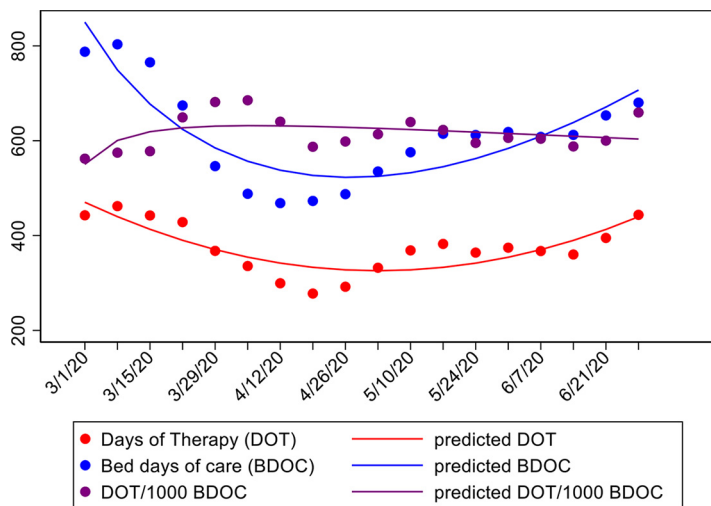
FIG 2 Weekly in-hospital antibiotic use and bed days of care, 1 March through 4 July 2020. Data are presented as 3-week rolling averages of numbers of in-hospital antibiotic days of therapy (DOT), bed days of care (BDOC), and DOT per 1,000 BDOC (y axis) each week (x axis; dates represent the first day of a given week). Lines connect predicted weekly values of a fractional polynomial fit for each of these measurements. There was no significant week-to-week difference in DOT, BDOC, and DOT per 1,000 BDOC over the entire time period. However, DOT and BDOC decreased significantly from 1 March through 2 May 2020 (25.6 DOT per week [5.1% weekly reduction {CI, 3.4% to 8.8%}; $P < 0.001$] and 49.5 BDOC per week [5.8% weekly reduction {CI, 3.4% to 8.8%}; $P < 0.001$]).

10.1%]; $P = 0.001$) (Fig. 1A). There was an adjusted average decrease of 285 BDOC per month for March to June 2020 (7.8% monthly reduction [CI, 4.4% to 11.3%]; $P < 0.001$) (Fig. 1B). Antibiotic DOT per 1,000 BDOC increased by an adjusted average of 8.1 per month for March to June 2020 (1.3% monthly increase [CI, 0.7% to 4.8%]; $P = 0.001$) (Fig. 1C).

Significant increases were observed in monthly DOT per 1,000 BDOC of non-antipseudomonal penicillins (monthly increase, 7.0 DOT/1,000 BDOC [CI, 5 to 9.2 DOT/1,000 BDOC]; $P < 0.001$) and macrolides (monthly increase, 3.6 DOT/1,000 BDOC [CI, 2.5 to 4.7 DOT/1,000 BDOC]; $P < 0.001$) (Fig. S1a and S1b). Decreases were observed in monthly DOT per 1,000 BDOC of antipseudomonal penicillins (monthly decrease, 7.8 DOT/1,000 BDOC [CI, 5.9 to 9.7]; $P < 0.001$), non-antipseudomonal cephalosporins (monthly decrease, 1.3 DOT/1,000 BDOC [CI, 0.04 to 2.89 DOT/1,000 BDOC]; $P = 0.06$), and fluoroquinolones (monthly decrease, 2.7 DOT/1,000 BDOC [CI, 1.5 to 3.9 DOT/1,000 BDOC]; $P = 0.001$) (data not shown). There was no change in DOT per 1,000 BDOC for antipseudomonal cephalosporins, carbapenems, anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) agents, aminoglycosides, and other agents.

From 1 March through 4 July 2020, there was no significant change in weekly antibiotic DOT ($P = 0.49$), BDOC ($P = 0.38$), or DOT per 1,000 BDOC ($P = 0.79$) (Fig. 2). For 1 March through 2 May 2020, however, antibiotic DOT and BDOC decreased by weekly averages of 25.6 (5.1% weekly reduction [CI, 3.4% to 8.8%]; $P < 0.001$) and 49.5 (5.8% [CI, 3.4% to 8.8%]; $P < 0.001$), respectively, before rebounding thereafter.

To understand COVID-19-related stewardship practices at VAPHS, we conducted a retrospective cohort study of consecutive inpatients who were diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection through 2 May 2020 (Palo Alto [CA] VA reverse transcription PCR assay through April 10, Aires assay [Luminex, Austin, TX] thereafter). Bacterial infections were diagnosed in 31% (5/16) of patients (Table S2). Antibiotics were administered to 56% (9/16) of patients during hospitalization. One hundred percent (9/9) of patients requiring ICU care received antibiotics, compared to 0% (0/7) of patients not requiring ICU care ($P = 0.0001$). Antibiotics were prescribed against infections present upon admission or acquired in-hospital (19% each [3/16]), or as short-term (≤4-days) empirical therapy (31% [5/16]).

Outcomes were survival to discharge (75% [12/16]), alive in hospital (12.5% [2/16]), and died in hospital (12.5%, 2/16).

To our knowledge, this is the first study of the volume of antibiotic consumption and COVID-19-related stewardship practices at a hospital outside of a disease epicenter during the early phase of the pandemic. Using a rigorous, monthly adjusted, interrupted time series regression analysis, we demonstrated that COVID-19 was associated with significant reductions in monthly antibiotic DOT and BDOC at VAPHS in March through June 2020 compared to previous years. Overall antibiotic DOT per 1,000 BDOC was significantly increased. In particular, there were significant increases in non-antipseudomonal penicillin and macrolide (i.e., azithromycin) DOT per 1,000 BDOC, agents recommended as first-line treatment for community acquired pneumonia (CAP) at our hospital. Notably, azithromycin was not used to treat COVID-19, other than as empirical therapy for CAP in two patients who also received amoxicillin-clavulanate or ceftriaxone (Table S2). Our findings are consistent with limited data from hospitals in the COVID-19 epicenters of Barcelona and Richmond, which showed increased use per patient day of azithromycin and either amoxicillin-clavulanate or ceftriaxone in March to April 2020 (4–6). Taken together, the few studies to date suggest that antibiotics were commonly prescribed for patients who presented with possible respiratory tract infections such as CAP at hospitals in both epicenters and non-epicenters. These prescription patterns likely reflect difficulties in distinguishing between CAP and COVID-19 based on signs and symptoms, as well as ongoing CAP hospital admissions during the COVID-19 pandemic. Monthly DOT per 1,000 BDOC of broad-spectrum agents such as antipseudomonal penicillins, non-antipseudomonal cephalosporins, and fluoroquinolones, which we commonly use to treat health care-associated pneumonia and other nosocomial infections, were significantly decreased at our hospital in March through June 2020. As the COVID-19 pandemic unfolds, temporal-spatial descriptions of antibiotic use from hospitals and regions with different epidemiologies will be crucial for accurate understanding of microbiology and antimicrobial resistance (AMR) trends.

Hospital utilization and antibiotic prescribing changed over the study. Weekly antibiotic DOT and BDOC were significantly decreased from 1 March through 2 May as COVID-19 restrictions were imposed at our hospital, and they gradually returned to baseline as previously suspended health care services were resumed. Antibiotic prescribing patterns were more likely driven by hospital census than by systematic changes in prescriber behavior. The impact of COVID-19 on AMR is presently uncertain. On the one hand, increased antibiotic use among patients admitted to the hospital (as evident by increased DOT per 1,000 BDOC) and COVID-19-related disruptions to public health services and infrastructure may promote the emergence or spread of AMR (7). On the other hand, reductions in overall antibiotic use (DOT), attention to infection prevention, and limitations on travel may be associated with decreased or stable AMR rates (8). It is likely that antibiotic prescription and AMR patterns will vary throughout the COVID-19 pandemic as numbers of cases fluctuate, and between epicenters and nonepicenters, by country and region, from hospital to hospital within regions, and within different hospital units (7).

Responsible stewardship will be crucial for limiting unnecessary antimicrobial usage and AMR during the pandemic. Our experience suggests that stewardship strategies should be targeted to 4 groups of hospitalized COVID-19 patients (Table 1). Our antibiotic use was consistent with sound stewardship practices, which promoted withholding treatment if there was no suspicion of bacterial infection (group 1; 44%), rapidly discontinuing empirical therapy once suspected coinfections such as CAP were excluded (group 2; 31%), and limiting durations of treatment for coinfections diagnosed upon presentation (group 3; 19%) or nosocomial secondary infections (group 4; 19%).

We acknowledge that our study is limited by its single-center nature and that the findings will not be applicable to all hospitals or stages of the pandemic. However, our experience highlights that COVID-19 will impact antibiotic usage in a dynamic fashion,

TABLE 1 Targeted antimicrobial stewardship strategies for patients hospitalized with COVID-19

Patient group (% of total)[a]	Rationale	Type of antimicrobial treatment	Stewardship goals
1. No evidence of coinfection or secondary infection (44)	Most patients with COVID-19 do well with supportive care, without use of antibiotics	None	Early stewardship interventions in emergency departments and on hospital floors to limit unnecessary antibiotic use, including use of rapid diagnostics
2. Presenting with possible coinfection (31)	Signs and symptoms of coinfections or secondary infections may be difficult to distinguish from those of COVID-19[b]	Empirical agents directed against most likely pathogens for infections such as community-acquired pneumonia and urinary tract infections	Rapid de-escalation of empirical antibiotics once COVID-19 is diagnosed and bacterial infection is excluded
3. Presenting with coinfection (19)[c]	Patients at increased risk for more-severe COVID-19, such as the elderly and those with underlying systemic diseases, suppressed immune systems, and living in closed, confined communities, are also often at increased risk for bacterial infections	Agents directed narrowly against known or most likely pathogens	Promote narrow-spectrum agents, short course regimens, and oral administration as feasible
4. Developing secondary infection while in hospital (19)	Hospitalized patients, in particular those who are critically ill, in ICUs, or receiving mechanical ventilation, are at increased risk for secondary infections, independent of COVID-19	Empirical agents directed against most likely pathogens for infections such as ventilator-associated pneumonia	Narrow coverage as quickly as possible; promote short course regimens as feasible to limit pressure for resistance and complications such as *Clostridioides difficile* infection

[a]Percentage of patients fitting into respective group. Note that the summed percentage exceeds 100% because 2 patients received short-course empirical therapy on admission (group 2) and then later were treated for hospital-acquired infections (ventilator-associated pneumonia) (group 4).
[b]Bacterial infection was defined as microbiologically confirmed infection with associated signs, symptoms, and, where relevant, imaging findings. Given the presentation of COVID-19, it may be difficult to definitively distinguish bacterial colonization from pneumonia in patients with respiratory symptoms. For our purposes, cases meeting the definition above were considered to be bacterial pneumonia, since the diagnosis could not be absolutely excluded.
[c]Two patients were diagnosed with bacterial infections (*Escherichia coli* urinary tract infection and *C. difficile* infection). A third patient presented with febrile neutropenia and facial swelling that was due to either cellulitis or hematoma. The patient is included in group 3, since he was treated for infection. This case was not included as a secondary bacterial infection in the text, since a definitive diagnosis was not established and a pathogen was not recovered.

including at hospitals and in regions removed from disease epicenters. It will be instructive to analyze epidemiologic, clinical, microbiologic, and AMR data at our hospital beginning in July 2020, as COVID-19 moved more aggressively into the Pittsburgh area. An advantage of the relatively low numbers of COVID-19 patients we encountered through June 2020 was that stewardship priorities identified in this study were in place as more patients were diagnosed with COVID-19.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.
SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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