Title: Antibiotic consumption and stewardship at a hospital outside of an early Coronavirus disease 2019 epicentre

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Abstract

There are scant data on impact of coronavirus disease (COVID)-19 on hospital antibiotic consumption, and no data from outside epicentres. At our non-epicentre hospital, antibiotic days of therapy (DOT) and bed days of care (BDOC) were reduced by 151.5/month and 285/month, respectively, for March-June 2020, compared to 2018-19 (P=0.001 and P<0.001). DOT/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.
The impact of coronavirus disease (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%-100% of those in intensive care units (ICUs) [1, 2]. The data suggest that COVID-19 might fuel antibiotic over-use. 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 healthcare 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 over 60% for 19-25 April 2020 compared with the same week in 2019 [3]. Studies from March and April 2020 at an adult and a paediatrics hospital in Barcelona, a major European COVID-19 epicentre, reported increased antibiotic days of therapy (DOT) per patient day [4, 5]. At a hospital in Richmond, an epicentre 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 paediatrics hospital [5]. Thus far, there are no data on antibiotic consumption in hospitals outside of a COVID-19 epicentre.

Our objective was to determine 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 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/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 Figure 1. DOT, BDOC and DOT/1,000 BDOC for March-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/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 Supplemental Table 1. During March-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 10.1%]; P=0.001) (Figure 1a). There was an adjusted average decrease of 285 BDOC per month for March-June 2020 (7.8% monthly reduction [CI: 4.4% to 11.3%]; P<0.001) (Figure 1b). Antibiotic DOT/1,000 BDOC increased by an adjusted average of 8.1 per month for March-June 2020 (1.3% monthly increase [CI: 0.7% to 4.8%]; P=0.001) (Figure 1c).

Significant increases were observed in monthly DOT/1,000 BDOC of non-antipseudomonal penicillins (7.0 DOT/1,000 BDOC monthly increase [CI: 5 to 9.2 DOT/1,000 BDOC]; P<0.001) and macrolides (3.6 DOT/1,000 BDOC monthly increase [CI: 2.5 to 4.7 DOT/1,000 BDOC]; P<0.001) (Supplemental Figures 1a and 1b). Decreases were observed in monthly DOT/1,000 BDOC of antipseudomonal penicillins (7.8 DOT/1,000 BDOC monthly decrease [CI: 5.9 to 9.7]; P<0.001), non-antipseudomonal cephalosporins (1.3 DOT/1,000 BDOC monthly decrease [CI: 0.04 to 2.89 DOT/1,000 BDOC]; P=0.06), and fluoroquinolones (2.7 DOT/1000 BDOC monthly decrease [CI: 1.5 to 3.9 DOT/1000 BDOC]; P=0.001) (data not available August 30, 2020 by guest http://aac.asm.org/Downloaded from.
shown). There was no change in DOT/1,000 BDOC for antipseudomonal cephalosporins, carbapenems, 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/1,000 BDOC (P=0.79) (Figure 2). For 1 March through 2 May 2020, however, antibiotic DOT and BDOC decreased by weekly averages of 25.6 (5.1%) 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 SARS-CoV-2 infection through 2 May 2020 (Palo Alto (CA) VA reverse transcription polymerase chain reaction assay through April 10, Aires assay (Luminex, Austin, TX) thereafter). Bacterial infections were diagnosed in 31% (5/16) of patients (Supplemental Table 2). 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) empiric 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 epicentre 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/1,000 BDOC was significantly increased. In particular, there were significant increases in non-antipseudomonal penicillin and macrolide (i.e.,
azithromycin) DOT/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 empiric therapy for CAP in two patients who also received amoxicillin-
clavulanate or ceftriaxone (Supplemental Table 2). Our findings are consistent with limited data
from hospitals in COVID-19 epicentres of Barcelona and Richmond, which showed increased
use per patient day of azithromycin and either amoxicillin-clavulanate or ceftriaxone in March-
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 epicentres and non-epicentres. These prescription patterns likely
reflect difficulties in distinguishing between CAP and COVID-19 based on signs and symptoms,
and ongoing CAP hospital admissions during the COVID-19 pandemic. Monthly DOT/1,000
BDOC of broad-spectrum agents like antipseudomonal penicillins, non-antipseudomonal
cephalosporins and fluoroquinolones, which we commonly use to treat healthcare 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 epidemiology 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 healthcare services were resumed. Antibiotic prescribing patterns were more likely
driven by hospital census than by systematic changes in prescriber behaviour. 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/1,000 BDOC) and COVID-19-
related disruptions to public health services and infrastructure may promote 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 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 epicentres and non-epicentres, 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 empiric therapy once suspected co-infections such as CAP were excluded (group 2, 31%), and limiting durations of treatment for co-infections 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 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 dynamic fashion, including at hospitals and in regions removed from disease epicentres. 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.
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| Patient group, % of total* | Rationale | Type of antimicrobial treatment | Stewardship goals |
|---------------------------|-----------|---------------------------------|-------------------|
| 1. No evidence of co-infection 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 co-infection, 31% | Signs and symptoms of co-infections or secondary infections may be difficult to distinguish from those of COVID-19** | Empiric agents directed against most likely pathogens for infections like community acquired pneumonia, urinary tract infections, etc. | Rapid de-escalation of empiric antibiotics once COVID-19 is diagnosed and bacterial infection is excluded. |
| 3. Presenting with co-infection, 19%*** | Patients at increased risk for more severe COVID-19, such as 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 | Empiric agents directed against most likely pathogens for infections like ventilator associated pneumonia | Narrow coverage as quickly as possible, and promote short course regimens as feasible to limit pressure for resistance and complications like C. difficile infection |

COVID-19: coronavirus disease 2019; ICU: intensive care unit

*Percentage of patients fitting into respective group. Note that summed percentage exceeds 100% since 2 patients received short-course empiric therapy on admission (group 2), and then later were treated for hospital-acquired infections (ventilator-associated pneumonia) (group 4).

**Bacterial infection was defined as microbiologically confirmed infection with associated signs, symptoms, and, where relevant, imaging findings. Given the presentation of COVID-19 disease, 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.

***Two patients were diagnosed with bacterial infections (E. coli UTI 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 Results section since a definitive diagnosis was not established and a pathogen was not recovered.
Legends to Figures

Figure 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). Figures 1a-1c show interrupted time series analyses, adjusted for month for DOT, BDOC and DOT/1,000 BDOC, respectively. In-hospital antibiotic DOT and BDOC in March-June 2020 were significantly reduced compared to previous months (P=0.001 and P<0.001, respectively). There was an increase in DOT/1,000 BDOC in March-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-anti-pseudomonal penicillins were defined as penicillin, amoxicillin, amoxicillin-clavulanate, oxacillin, nafcillin, and ampicillin-sulbactam. Non-anti-pseudomonal cephalosporins were defined as cefazolin, cephalaxin, cefadroxil, cefuroxime, cefoxitin, ceftriaxone, and cefdinir. Anti-pseudomonal penicillins were defined as piperacillin-tazobactam and aztreonam. Anti-pseudomonal cephalosporins were defined as ceftazidime, cefepime, ceftolozane-tazobactam and ceftazidime-avibactam. Anti-methicillin resistant Staphylococcus aureus (MRSA) agents were defined as vancomycin, daptomycin, linezolid, and ceftaroline.

Figure 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/1,000 BDOC over the entire time period. However, DOT and BDOC significantly decreased 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% [CI: 3.4% to 8.8%]; \( P < 0.001 \), respectively).
Figure 1a.

![Graph showing antibiotic days of therapy (DOT) from 1/18 to 5/20 with actual and predicted data points.](image-url)
Figure 2.