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Change in Antimicrobial Use During COVID-19 Pandemic in South Carolina Hospitals: A Multicenter Observational Cohort Study



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ABSTRACT

Objectives: This retrospective cohort study examined the impact of the pandemic on antimicrobial use (AU) in South Carolina hospitals.

Methods: Antimicrobial use in days of therapy (DOT) per 1000 days-present was evaluated in 17 hospitals in South Carolina. Matched-pairs mean difference was used to compare AU during the pandemic (March–June 2020) with that during the same months in 2019 in hospitals that did and did not admit patients with COVID-19.

Results: There was a 6.6% increase in overall AU in the seven hospitals that admitted patients with COVID-19 (from 530.9 to 565.8; mean difference (MD) 34.9 DOT/1000 days-present; 95% CI 4.3, 65.6; $P = 0.03$). There was no significant change in overall AU in the remaining 10 hospitals that did not admit patients with COVID-19 (MD 6.0 DOT/1000 days-present; 95% CI –55.5, 67.6; $P = 0.83$). Most of the increase in AU in the seven hospitals that admitted patients with COVID-19 was observed in broad-spectrum antimicrobial agents. A 16.4% increase was observed in agents predominantly used for hospital-onset infections (from 122.3 to 142.5; MD 20.1 DOT/1000 days-present; 95% CI 11.1, 29.1; $P = 0.002$). There was also a 9.9% increase in the use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents (from 66.7 to 73.3; MD 6.6 DOT/1000 days-present; 95% CI 2.3, 10.8; $P = 0.01$).

Conclusion: The COVID-19 pandemic appears to drive overall and broad-spectrum antimicrobial use in South Carolina hospitals admitting patients with COVID-19. Additional antimicrobial stewardship resources are needed to curtail excessive antimicrobial use in hospitals to prevent subsequent increases in antimicrobial resistance and *Clostridioides difficile* infection rates, given the continuing nature of the pandemic.

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1. Introduction

Due to the novel nature of the COVID-19 pandemic, little was initially known regarding bacterial co-infection rates with this viral pneumonia. Early in the pandemic, up to three-quarters of hos-

pitalised adults with COVID-19 were prescribed empiric antibacterial agents [1–3]. As the pandemic progressed, evidence emerged that bacterial co-infections ranged from 3.5–8.1% in hospitalised patients with COVID-19 [3–6]. Within the United States, there were notable increases in antimicrobial prescribing rates, including broad-spectrum antimicrobials, with more severe COVID-19 disease presentation [3].

Antimicrobial stewardship programs (ASPs) are critical components of hospital safety and quality teams, as they play an essential role in developing local treatment guidelines and assisting front-

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line healthcare providers [7]. ASPs have longstanding roles in optimising selection of empiric antimicrobial therapy and assisting with targeted de-escalation [8]. However, during the initial days of the pandemic, many ASP resources were repurposed to support the needs of healthcare systems during the pandemic, limiting their time for dedicated ASP initiatives [9]. This reprioritisation of ASP workflow, the lack of clinical data, and modifications in ASP team dynamics with frontline providers during the pandemic created the potential for amplification of inappropriate antimicrobial prescribing [9].

This multicentre, retrospective, observational cohort study aimed to compare overall and broad-spectrum antimicrobial use during the pandemic (March–June 2020) with the same months of the previous year in hospitals that admitted patients with COVID-19 and those that did not admit patients with COVID-19 in South Carolina.

2. Materials and methods

2.1. Settings

All 22 hospitals in South Carolina that submitted antimicrobial use data to the National Healthcare Safety Network (NHSN) in March–June 2019 and March–June 2020, and gave permission to the South Carolina Department of Health and Environmental Control and the Antimicrobial Stewardship Collaborative of South Carolina to access their antimicrobial use data, were invited to participate in this study.

2.2. Data collection

Overall antimicrobial use for all antibacterial agents, broad-spectrum antibacterial agents predominantly used for hospital-onset infections, broad-spectrum antibacterial agents predominantly used for community-acquired infections, and antibacterial agents predominantly used for resistant Gram-positive infections were collected from the NHSN's antimicrobial use option.

2.3. Definitions

Broad-spectrum antibacterial agents predominantly used for hospital-onset infections included antipseudomonal penicillins, cephalosporins, carbapenems, and aminoglycosides. Broad-spectrum agents predominantly used for community-acquired infections included third-generation cephalosporins and fluoroquinolones. Antibacterial agents predominantly used for resistant Gram-positive infections included vancomycin and other agents with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [10]. From the NHSN, standardised antimicrobial administration ratios (SAARs), a ratio of reported antimicrobial days over statistically modelled antimicrobial days, were also included to more easily compare AU between hospitals [11].

2.4. Statistical analysis

Antimicrobial use in days of therapy (DOT) per 1000 days-present was evaluated. Matched-pairs mean difference was used to compare antimicrobial use during the pandemic (March–June 2020) and the same time period in the previous year (March–June 2019) in hospitals that did and did not admit patients with COVID-19 in March–June 2020. JMP Pro (version 13.0, SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis. The level of significance for statistical testing was defined as two-sided $P < 0.05$.

3. Results

3.1. Characteristics of participating hospitals

Seventeen of the 22 invited hospitals (77%) agreed to participate in the study. Of the 17 included hospitals in the analysis, seven admitted patients with COVID-19 in March–June 2020 and the remaining 10 did not. Hospitals that admitted patients with COVID-19 were relatively larger, more likely to have in-house ASPs (a pharmacist or physician available within that hospital), and had lower baseline SAARs in 2019 than comparators (Table 1).

3.2. Antimicrobial use in hospitals that admitted patients with COVID-19

In the seven hospitals that admitted patients with COVID-19, there was a significant increase in overall antimicrobial use during the pandemic (mean difference (MD) 34.9 DOT/1000 days-present; 95% CI 4.3, 65.6; $P = 0.03$; Figure 1). This corresponded to a 6.6% increase in overall antimicrobial use from March–June 2019 to the same months in 2020. Most of the increase in antimicrobial use in these seven hospitals was observed in broad-spectrum agents predominantly used for hospital-onset infections (16.4% increase from 122.3 in 2019 to 142.5 DOT/1000 days-present in 2020). There was also a 9.9% increase in the use of broad-spectrum Gram-positive agents in these seven hospitals from 66.7 to 73.3 DOT/1000 days-present.

3.3. Antimicrobial use in hospitals that did not admit patients with COVID-19

There were no significant changes in overall antimicrobial use, broad-spectrum agents predominantly used for hospital-onset infections, or broad-spectrum Gram-positive agents in hospitals that did not admit patients with COVID-19. Conversely, there was a significant decline in antimicrobial use of broad-spectrum agents predominantly used for community-acquired infections in these hospitals in March–June 2020 compared with 2019 (Table 1; Figure 1).

4. Discussion

4.1. Antimicrobial use during the pandemic

There was a significant increase in the overall antimicrobial use in the South Carolina hospitals that admitted patients with COVID-19 during the pandemic when compared with the same time period in the previous year. Increases were specifically observed in the use of broad-spectrum agents, particularly anti-pseudomonal beta-lactams and anti-MRSA agents. Interestingly, similar increases in antimicrobial use were not demonstrated in hospitals that did not admit patients with COVID-19. Treating patients with COVID-19 appears to drive overall and broad-spectrum antimicrobial use in hospitals.

The COVID-19 pandemic has imposed unprecedented challenges on ASPs and threatened to erase the gains made in this field over the past few years. A multicentre cohort study of 84 Veterans Administration hospitals in the United States recently reported a decline in antimicrobial use from 2015 through 2019 [12]. However, the increase in antimicrobial use observed in January–May 2020 negated the prior years of antimicrobial stewardship improvements [12]. Reports of increased antimicrobial use early in the COVID-19 pandemic also emerged from single medical centres in the United States and Singapore [13–15]. It is believed that this is the first study to contrast the change in antimicrobial use during the pandemic in hospitals that did and did not admit patients with COVID-19.

Table 1
Hospital characteristics and antimicrobial use in March–June 2019 and 2020 in hospitals that admitted COVID-19 and non-COVID-19 patients.

Variable	Hospitals that admitted COVID-19 patients(n=7)	Hospitals that did not admit COVID-19 patients (n=10)
Bed size, n (%)		
< 200	1 (14)	9 (90)
200–499	3 (43)	1 (10)
≥ 500	3 (43)	0 (0)
In-house ASP, n (%)	7 (100)	5 (50)
Hospital occupancy		
Mean hospital days present in 2019	27 642	6364
Mean hospital days present in 2020	22 657	5114
Mean SAAR (95% CI): all antimicrobial agents in all adult locations		
2019	0.84 (0.70, 0.98)	1.07 (0.93, 1.22)
2020	0.92 (0.76, 1.07)	1.08 (0.95, 1.21)
Overall AU for all antimicrobials		
Mean AU in 2019	530.9	647.0
Mean AU in 2020	565.8	653.0
Broad-spectrum agents used for hospital-onset infections		
Mean AU in 2019	122.3	172.1
Mean AU in 2020	142.5	168.9
Broad-spectrum agents used for community-acquired infections		
Mean AU in 2019	110.4	176.0
Mean AU in 2020	119.5	157.8
Agents used for resistant Gram-positive infections		
Mean AU in 2019	66.7	90.1
Mean AU in 2020	73.3	83.0

Abbreviations: ASP, antimicrobial stewardship program; SAAR, standardised antimicrobial administration ratio; CI, confidence intervals; AU, antimicrobial use
Antimicrobial use is reported in days of therapy per 1000 days-present

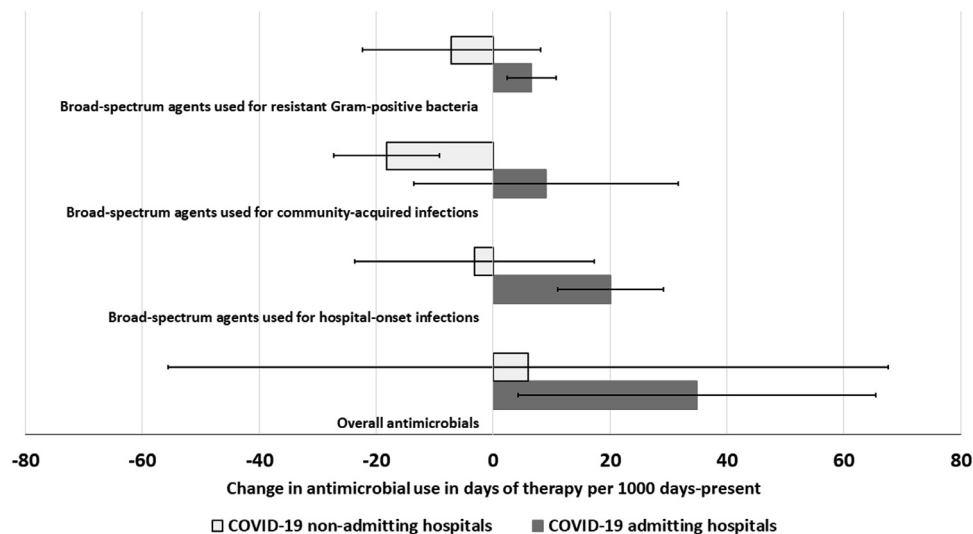


Figure 1. Mean change in antimicrobial use in March–June 2020 compared with March–June 2019. Error bars indicate 95% confidence intervals

4.2. Potential consequences of increased antimicrobial use

The increase in overall antimicrobial use during the pandemic is concerning. However, the steeper rise in the use of broad-spectrum agents in hospitals that admitted patients with COVID-19 is even more alarming. These results are consistent with a recent large review reporting that > 70% of patients with COVID-19 received antimicrobials, the majority being broad-spectrum antibacterial agents [2,4]. This is despite the low incidence of bacterial co-infection, ranging from 5.9% in all hospitalised patients to 8.1% in critically ill patients, with bacterial superinfections re-

ported as high as 20% [4,16]. The most common organisms identified in superinfections include *Acinetobacter* spp., *Pseudomonas*, and *Escherichia coli*, indicating likely need for broad-spectrum coverage; however, the risks of these agents must be considered [16]. The increasing use of broad-spectrum agents predominantly used for hospital-onset infections in the current study is particularly concerning for antimicrobial stewards, given the high risk of hospital-onset *Clostridioides difficile* infections associated with the heavy use of these broad-spectrum agents [8,17]. Although some aspects of infection prevention, such as hand hygiene, personal protective equipment, and environmental hygiene, are heightened, other

risks for nosocomial spread of infection have lessened monitoring, such as contact isolation, admission screening, and ASP [9]. In New York City, worsening *Enterobacteriales* susceptibility rates during the pandemic were observed compared with data from 2018–2019 [5]. The spread of carbapenem-resistant Gram-negative bacteria and *Candida auris* was described in acute care hospitals and intensive care units during the peak of the pandemic in Italy and the United States [18–20]; specific lapses in standard infection prevention practices were noted [20].

4.3. Unique antimicrobial stewardship challenges

In addition to increased antimicrobial use in hospitalised patients with COVID-19, other structural changes to ASP during the pandemic likely influenced the study results. Stevens and colleagues discussed the many roles that ASP members may play in COVID-19 response efforts, including assisting with creating treatment guidelines and facilitating the use of medications approved by emergency-use authorisation [7]. In South Carolina, many ASP members had their workloads redirected towards other duties like procuring and facilitating remdesivir usage, as well as developing guidelines for its usage and covering non-ASP-related tasks for pharmacy furloughs. Diversion of ASP resources may also limit the effectiveness of antimicrobials post-prescription audit and feedback interventions. Although all hospitals that admitted patients with COVID-19 in South Carolina had in-house ASP and robust baseline antimicrobial use metrics based on 2019 SAAR data, they were not immune to the great challenges posed by the COVID-19 pandemic. All these factors likely contributed to higher overall and broad-spectrum antimicrobial use during the pandemic in hospitals that admitted patients with COVID-19. It is speculated that less disruption in the daily workflow of ASPs likely resulted in stable overall antimicrobial use during the pandemic in hospitals that did not admit patients with COVID-19, and even a decline in one category, possibly due to ongoing efforts to reduce already high baseline antimicrobial use.

4.4. Strengths and limitations

The multicentre design and accounting for seasonal variation in antimicrobial use by comparing March–June 2020 with the same months in 2019 were major strengths of this study. The study shares common limitations of observational cohorts, including not accounting for unknown or unmeasured confounders. In addition, the study examined quantitative antimicrobial use in hospitals and did not include patient-level data to assess appropriateness, including potential increases in intensive care populations during the COVID-19 pandemic or decreases in AU due to cancelled elective procedures. There is speculation about sicker populations making up hospital admissions other than COVID-19 patients during the pandemic, affecting antimicrobial use, but this has not yet been quantified. In one study of hospital admissions during the pandemic, largely flat mortality rates implied that total in-hospital deaths decreased on par with decreased in-hospital admissions, so the assumption of sicker patients still seeking medical care may not bear out [21]. It remains undetermined whether the increase in antimicrobial use in hospitals that admitted COVID-19 patients was mostly due to excessive antimicrobial use in patients with COVID-19 or disruption of routine antimicrobial stewardship activities. The proportion of hospital admissions due to COVID-19 early in the pandemic was not available in most hospitals that admitted COVID-19 patients. There was a numerical overall decline in hospital occupancy in all participating hospitals in the study – this was likely due to suspension of elective procedures and other mitigation policies early in the pandemic in South Carolina. The specific

impact of these changes on patient demographics were not measured in this study. Finally, the study was confined to a specific geographical area so the results may not be generalisable to other regions.

5. Conclusions

A significant increase in overall and broad-spectrum antimicrobial use was observed in hospitals that admitted patients with COVID-19 in South Carolina. The pandemic continues to stress and test the resilience of healthcare systems and ASPs alike. At a time when resources may be limited, keeping the focus on patient safety and quality teams within hospitals is more important than ever before. Healthcare providers must continue to work together towards judicious antimicrobial use in the face of the developing knowledge regarding COVID-19.

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Ethical Approval

The study was approved by the University of South Carolina Institutional Review Board (Columbia, SC, USA).

Declarations of Competing Interests

PB, JK, CMF, SU, EL, LS, SW, and MNA: no conflicts
HRW: bioMérieux, Speaker's Bureau (nonbranded content); JJ: bioMérieux, Speaker's Bureau (nonbranded content), Merck, Advisory Board; PBB: bioMérieux, Speaker's Bureau (nonbranded content), Kedrion Biopharma Advisory Board, research grant.

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HRW and MNA had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the analysis.

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