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MAJOR ARTICLE

A Multicenter Comparison of Prevalence and Predictors of Antimicrobial Resistance in Hospitalized Patients Before and During the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic

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Background. Antibacterial therapy is frequently used in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) without evidence of bacterial infection, prompting concerns about increased antimicrobial resistance (AMR). We evaluated trends in AMR before and during the SARS-CoV-2 pandemic.

Methods. This multicenter, retrospective cohort analysis included hospitalized adults aged ≥18 years with >1-day inpatient admission and a record of discharge or death from 271 US facilities in the BD Insights Research Database. We evaluated rates of AMR events, defined as positive cultures for select gram-negative and gram-positive pathogens from any source, with nonsusceptibility reported by commercial panels before (1 July 2019–29 February 2020) and during (1 March 2020–30 October 2021) the SARS-CoV-2 pandemic.

Results. Of 5 518 666 admissions evaluated, AMR rates per 1000 admissions were 35.4 for the prepandemic period and 34.7 for the pandemic period ($P \leq .0001$). In the pandemic period, AMR rates per 1000 admissions were 49.2 for SARS-CoV-2–positive admissions, 41.1 for SARS-CoV-2–negative admissions, and 25.7 for patients untested ($P \leq .0001$). AMR rates per 1000 admissions among community-onset infections during the pandemic were lower versus prepandemic levels (26.1 vs 27.6; $P < .0001$), whereas AMR rates for hospital-onset infections were higher (8.6 vs 7.7; $P < .0001$), driven largely by SARS-CoV-2–positive admissions (21.8). AMR rates were associated with overall antimicrobial use, rates of positive cultures, and higher use of inadequate empiric therapy.

Conclusions. Although overall AMR rates did not substantially increase from prepandemic levels, patients tested for SARS-CoV-2 infection had a significantly higher rate of AMR and hospital-onset infections. Antimicrobial and diagnostic stewardship is key to identifying this high-risk AMR population.

Keywords. antibiotics; antimicrobial stewardship; antimicrobial resistance; COVID-19; nosocomial infections.

Increasing antimicrobial resistance (AMR) represents an urgent threat to public health. In 2019 alone, it was estimated that bacterial AMR resulted in 4.95 million deaths globally [1]. In the United States (US), resistant bacteria and fungi appear to be responsible for at least 3 million new infections annually [2]. The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has disrupted healthcare systems, infection prevention efforts, and stewardship practices, leading to concerns about increasing AMR, particularly in the inpatient setting [3–7]. Underlying factors that may contribute to changes in AMR during the pandemic include the high intensity of care with invasive devices needed for patients with COVID-19, longer lengths of stay, and most importantly, a high rate of antimicrobial use (AU) in patients who have relatively few coinfections or secondary bacterial infections [8]. While recent estimates suggest that only 3%–15% of patients with COVID-19 have microbial coinfections, up to 75%–80% of patients receive empirical antimicrobial therapy, setting the stage for increasing AMR [9–12].

Several recent reports have suggested an increase in AMR organisms during the COVID-19 pandemic, particularly in sites with a high burden of severe or critical COVID-19 [4, 8, 13–16]. For example, a retrospective study of patients in an Italian intensive care unit (ICU) found that the incidence of carbapenem-resistant Enterobacterales colonization increased from 6.7% in 2019 to 50% in March to April 2020 [16]. Reviews have suggested an unexpectedly high incidence of

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methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant Enterobacteriaceae, and *Candida auris* infections among patients admitted to the ICU during the pandemic [7]. However, most available evidence on pandemic AMR has been derived from case reports, case series, and single-center observational studies, making it difficult to assess the extent to which COVID-19 has affected AMR on a larger scale [7]. Because most studies have also focused on AMR patterns in the ICU, additional information on AMR in the overall inpatient population is needed [7]. Moreover, because most AMR analyses were conducted relatively early in the pandemic, the influence of COVID-19 therapeutics, vaccinations, and variants on AMR has yet to be thoroughly evaluated.

The goal of our study was to evaluate changes in AMR rates in bacteria in the US before and during the COVID-19 pandemic among inpatients admitted to facilities included in the BD Insights Research Database. We also evaluated the impact of SARS-CoV-2 status on these trends and assessed factors associated with higher AMR rates prior to and during the pandemic.

METHODS

Study Design

We conducted a multicenter, retrospective cohort analysis of all hospitalized adults aged ≥18 years from 271 US facilities included in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, New Jersey), which includes both small and large medical care facilities in rural and urban areas throughout the US (Supplementary Table 1). This retrospective, de-identified data set, which has been previously described [17–21], was approved and informed consent requirements were waived by the New England Institutional Review Board (Wellesley, Massachusetts). This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies [22].

Eligible admissions included subjects with a 1- to 365-day inpatient stay and a record of discharge or death between 1 July 2019 and 30 October 2021. All admissions with an AMR event (defined in Table 1), defined as a noncontaminated first positive culture for gram-negative (GN) and gram-positive (GP) pathogens of interest from respiratory, blood, urine, skin/wound, intraabdominal, or other source, were included in the analysis. For the purposes of comparison, patient admissions were categorized into 4 groups: (1) prepandemic (1 July 2019–29 February 2020) and during the SARS-CoV-2 pandemic (1 March 2020–30 October 2021); (2) SARS-CoV-2 positive; (3) SARS-CoV-2 negative; and (4) SARS-CoV-2 not tested.

Microbiology results likely associated with a contaminant were excluded by a previously described methodology that used source, time of collection, microorganism type, and number of microorganisms in a culture to flag likely contaminated samples [23]. AMR was evaluated in cultures with GN pathogens for Enterobacterales (*Citrobacter freundii*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, *Morganella morganii*, *Proteus mirabilis*, *Providencia stuartii*, *Serratia marcescens*), *Acinetobacter baumannii* spp, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*, and for GP pathogens (*Enterococcus* spp, *S aureus*, and *Streptococcus pneumoniae*) (Table 1) [18, 19].

AMR was calculated at the admission level by identifying admissions with a first positive culture with any of the above AMR pathogens of interest per 1000 admissions. AMR rates were evaluated overall and were defined as community onset (CO) if the first positive AMR event culture was collected ≤2 days from admission (day 1) and defined as hospital onset (HO) if the culture was collected >2 days after admission. All microbiology testing was performed by local microbiology laboratories in the cohort of hospitals included in the BD Insights Research Database.

Statistical Analysis

In the exploratory phase of the analysis, we generated descriptive tables comparing AMR and AU by SARS-CoV-2 testing status to AMR and AU in the pre–SARS-CoV-2 pandemic period. The overall descriptive statistics include rate of AMR per 1000 admissions, AU duration, SARS-CoV-2 burden, and SARS-CoV-2 testing status as well as measures for patient and hospital risk factors. Descriptive statistics were reported for resistance types (Table 1) including GN (carbapenem nonsusceptible [NS], extended-spectrum β-lactamase [ESBL] positive, piperacillin-tazobactam [Pip-Tazo] NS, and fluroquinolone [FQ] NS), multidrug-resistant (MDR) or pan-NS, and GP (methicillin-resistant *S aureus* [MRSA], vancomycin-resistant enterococci [VRE], and *S pneumoniae* any NS).

In the analysis phase, generalized linear mixed models with logistic regression were used to calculate the odds of AMR and AU by SARS-CoV-2 testing status as compared to the pre–SARS-CoV-2 period at the patient level with facility as a random effect. AMR models were run for patients with a GN or GP pathogen and were split by community and hospital onset. AU models consisted of all admissions and were split by those with a GN/GP pathogen and those with a negative pathogen or no culture collected. AMR models were adjusted for resistance type (GN/GP), inadequate therapy within 48 hours of culture collection [18], and AU duration. All models were adjusted for age, sex, prior admissions, underlying conditions, ventilation, admission to ICU, census region, and other facility characteristics (Supplementary Table 2). Analyses were conducted using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with RStudio (Boston, Massachusetts).

RESULTS

This study evaluated 1 789 458 patient admissions before the SARS-CoV-2 pandemic (1 July 2019–29 February 2020) and

Table 1. Definitions of Antimicrobial Resistance

Classification	Pathogen Type	Definition of Resistance
Gram-negative pathogens	ENT (*Citrobacter freundii*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, *Morganella morganii*, *Proteus mirabilis*, *Providencia stuartii*, *Serratia marcescens*), ACB, PsA, and *Stenotrophomonas maltophilia*	• ESBL-producing phenotype: *E coli*, *K pneumoniae*, *K oxytoca*, and *P mirabilis* isolates confirmed as ESBL positive per commercial panels or based on a result of I or R to antimicrobial susceptibility tests with ESC (ceftriaxone, cefotaxime, ceftazidime, or cefepime) • Pip-Tazo: I or R to Pip-Tazo • Carbapenem NS: I or R to ETP, IMI (excluded for *P mirabilis* and *M morganii*), MER, or DOR ◦ PsA and ACB if I or R to IMI, MER, or DOR ◦ *S maltophilia*: all presumed to be NS • FQ NS (I or R to ciprofloxacin, levofloxacin, or moxifloxacin [excluded for PsA/ACB]) • Multidrug resistance: MDR ENT, ACB, or PsA if I or R to at least 1 drug in 3 of the following 5 classes: ESC (cefotaxime [excluded for PsA/ACB], ceftriaxone [excluded for PsA/ACB], cefepime, or ceftazidime), FQ (ciprofloxacin, levofloxacin, or moxifloxacin [excluded for PsA/ACB]), aminoglycosides, carbapenems (ETP [excluded for PsA/ACB], IMI, MER, or DOR), and piperacillin or Pip-Tazo
Gram-positive pathogens	*Enterococcus* spp, (VRE), MRSA, and *Streptococcus pneumoniae*	• Enterococcus spp (VRE), *Staphylococcus aureus* (MRSA) • *S pneumoniae* to: ◦ Penicillin resistance: I or R to penicillin ◦ Macrolide resistance: I or R to erythromycin, azithromycin, or clarithromycin ◦ FQ resistance: I or R to levofloxacin or moxifloxacin ◦ Extended-spectrum cephalosporin resistance: I or R to ceftriaxone, cefotaxime, or cefepime ◦ Tetracycline resistance: I or R to doxycycline or tetracycline

Abbreviations: ACB, *Acinetobacter baumannii* species; DOR, doripenem; ESC, extended-spectrum cephalosporins; ENT, Enterobacterales; ESBL, extended-spectrum β-lactamase; ETP, ertapenem; FQ, fluoroquinolone; I, intermediate susceptibility; IMI, imipenem; MDR, multidrug-resistant; MER, meropenem; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, nonsusceptible; Pip-Tazo, piperacillin-tazobactam; PsA, *Pseudomonas aeruginosa*; R, resistant susceptibility; VRE, vancomycin-resistant enterococci.

3 729 208 patient admissions during the SARS-CoV-2 pandemic (1 March 2020–30 October 2021), of which 5.1% (189 114) were SARS-CoV-2 positive. Overall patient admissions to the ICU were significantly lower during the pandemic (11.6%) compared to the prepandemic period (11.9%) ($P < .001$), but ICU length of stay (LOS) was significantly higher during the pandemic ($P < .001$) and both were significantly higher for SARS-CoV-2–positive patients (20.8% of SARS-CoV-2–positive patients admitted to the ICU with median LOS of 5 days, versus 2 days prepandemic; $P < .001$ for both; Table 2).

AMR Rates Pre- and Postpandemic and by SARS-CoV-2 Test Status

Antimicrobial resistance was detected in 63 263 patient admissions (35.4/1000 admissions) in the prepandemic period and in 129 410 patient admissions (34.7/1000 admissions) during the pandemic ($P \leq .001$). Patient admissions tested for SARS-CoV-2 had a significantly higher AMR rate than that observed in prepandemic admissions (49.2 in SARS-CoV-2 positive and 41.1 in SARS-CoV-2 negative per 1000 admissions; $P < .001$ for both vs prepandemic period).

The CO AMR rate was significantly lower during the pandemic compared to the prepandemic period (26.1 vs 27.6 per 1000 admissions; $P < .001$); however the CO AMR rate was significantly higher during the pandemic for SARS-CoV-2–negative patients (31.1 vs 27.6 per 1000 admissions; $P < .001$). The HO AMR rate was also significantly higher during the pandemic compared to the prepandemic period (8.64 vs 7.74 per 1000 admissions; $P < .001$; Table 2). Patient admissions tested for SARS-CoV-2 had a significantly higher HO AMR rate per 1000 admissions compared to the rate among prepandemic admissions (21.8 in SARS-CoV-2 positive vs 10.0 in SARS-CoV-2 negative; $P < .001$ for both vs prepandemic period).

When examining resistance by bacterial type, only ESBL-positive ($ESBL^+$) and VRE rates per 1000 admissions were significantly higher during the pandemic compared to the prepandemic period (2.45 vs 2.15 for $ESBL^+$ and 1.59 vs 1.36 for VRE, respectively; $P < .001$; Table 3) and significantly higher in both CO and HO settings ($P < .001$ for all). However, for GN pathogens, Pip-Tazo NS, FQ NS, and MDR/pan-β-lactam resistance rates were significantly lower ($P < .001$ for all; Supplementary Table 3). For GP pathogens, resistance to *S pneumoniae* and *S aureus* was significantly lower ($P < .001$ for both) during the pandemic, but MRSA rates were significantly higher in SARS-CoV-2-positive

Table 2. Characteristics of Admissions During the Pre–Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pandemic Period and by SARS-CoV-2 Testing Status During the Pandemic

Characteristic	July 2019–Feb 2020 Pre–SARS-CoV-2	SARS-CoV-2 (March 2020–October 2021)			
		SARS-CoV-2 Positive	SARS-CoV-2 Negative	Not Tested	SARS-CoV-2 Period Total
Total admissions, No.	1 789 458	189 114	1 898 651	1 641 443	3 729 208
Total with ≥1 AMR event overall, No.	63 263	9296	77 999	42 115	129 410
Community onset	49 420	5164	59 024	33 000	97 188
Hospital onset	13 843	4132	18 975	9115	32 222
AMR rate per 1000 admissions	35.4	49.2*	41.1*	25.7*	34.7**
Community onset	27.6	27.3*	31.1*	20.1*	26.1**
Hospital onset	7.7	21.8*	10.0*	5.6*	8.6**
Total antibacterial DOT per 1000 d present	323.5	420.9*	360.3*	280.4*	334.1**
% of all admissions prescribed antibacterial therapy	35.0%	57.8%*	40.1%*	30.4%*	36.7%**
Antibacterial therapy duration, d, avg ± SD (median)	3.57 ± 4.43 (2)	5.68 ± 5.97 (4)*	3.92 ± 4.87 (3)*	3.28 ± 4.19 (2)*	3.80 ± 4.75 (2)**
% of admissions with a GN/GP pathogen of interest	9.3%	11.93%*	10.96%*	7.20%*	9.35%
Antibacterial therapy duration, d, avg ± SD (median)	6.25 ± 6.51 (4)	9.58 ± 9.08 (7)*	6.78 ± 7.11 (5)*	5.63 ± 6.14 (4)*	6.59 ± 7.03 (5)**
% antibacterial therapy duration ≥72 h	68.85%	79.20%*	72.11%*	63.02%*	69.49%**
% with GN/GP pathogen prescribed antibacterial therapy	86.08%	89.86%*	88.03%*	82.77%*	86.37%
% of admissions with a negative/no culture result[a]	90.7%	88.1%*	89.0%*	92.8%*	90.6%
Antibacterial therapy duration, d, avg ± SD (median)	2.98 ± 3.57 (2)	4.88 ± 4.72 (4)*	3.24 ± 3.85 (2)*	2.85 ± 3.56 (2)*	3.20 ± 3.84 (2)**
% antibacterial therapy duration ≥72 h	17.6%	41.1%*	21.0%*	14.9%*	19.2%**
% prescribed antibacterial therapy	29.72%	53.50%*	34.20%*	26.31%*	31.59%**
% IET in GN/GP admissions	20.20%	25.92%*	20.36%*	19.72%*	20.55%**
% IET in AMR admissions	34.46%	37.6%*	35.6%*	33.8%*	35.21%**
Age, y, avg ± SD (median)	58.39 ± 19.67 (61)	61.45 ± 17.91 (63)*	58.53 ± 19.71 (62)*	57.46 ± 19.73 (60)*	58.21 ± 19.65 (61)
Male sex, %	43.13%	50.24%*	43.84%*	42.96%*	43.78%**
Admissions with ≥1 comorbidity, %	47.13%	78.39%*	55.45%*	44.57%	51.83%**
Hospital LOS, d, avg ± SD (median)	4.26 ± 5.84 (3)	7.95 ± 10.47 (5)*	4.77 ± 7.02 (3)*	3.92 ± 6.28 (2)*	4.56 ± 6.98 (3)**
ED admission, %	33.68%	49.74%*	37.29%*	32.47%*	35.8%**
ICU admission, %	11.94%	20.84%*	12.67%*	9.35%*	11.62%**
ICU LOS, d, avg ± SD (median)	3.50 ± 4.68 (2)	8.18 ± 9.70 (5)*	3.95 ± 5.86 (2)*	3.37 ± 4.82 (2)*	4.13 ± 5.99 (2)**
Ventilated, %	1.11%	6.22%	1.7%*	0.83%*	1.55%**
Prior 30-d admission, %	10.64%	9.01%	11.05%*	10.7%	10.80%**
Prior 90-d admission, %	16.97%	13.84%	19.15%*	18.17%*	18.45%**

Abbreviations: AMR, antimicrobial resistance; avg, average; d, days; DOT, days of therapy; ED, emergency department; GN, gram-negative; GP, gram-positive; ICU, intensive care unit; IET, inadequate empiric therapy; LOS, length of stay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; y, years.

[a]Also includes admissions positive for a GN/GP pathogen not included as a pathogen of interest (1.16% of admissions).

*$P < .001$ using bivariate analysis of variance and χ^2 tests for group differences compared to pre–SARS-CoV-2.

**$P < .001$ using t test and χ^2 tests comparing SARS-CoV-2 total and pre–SARS-CoV-2 periods.

Table 3. Hospital-Onset and Community-Onset Antimicrobial Resistance Types per 1000 Admissions During the Pre–Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pandemic Period and by SARS-CoV-2 Testing Status During the Pandemic

Characteristic	July 2019–Feb 2020 Pre–SARS-CoV-2	SARS-CoV-2 (March 2020–October 2021)			
		SARS-CoV-2 Positive	SARS-CoV-2 Negative	Not Tested	SARS-CoV-2 Period Total
Total admissions, No.	1 789 458	189 114	1 898 651	1 641 443	3 729 208
Total with ≥1 AMR event overall, No.	63 263	9296	77 999	42 115	129 410
Resistance type, rate (No.)					
Gram-negative					
Carbapenem NS	0.807 (1444)	1.719 (325)*	0.920 (1747)*	0.548 (899)*	0.797 (2971)
ESBL positive	2.152 (3851)	3.659 (692)*	2.880 (5468)*	1.811 (2972)*	2.449 (9132)*
Pip-Tazo NS	1.122 (2008)	1.465 (277)*	1.199 (2277)	0.754 (1238)*	1.017 (3792)*
FQ NS	9.640 (17 250)	11.744 (2221)*	10.447 (19 836)*	7.092 (11 641)*	9.036 (33 698)*
MDR/pan-NS	10.835 (19 389)	15.874 (3002)*	12.947 (24 582)*	7.632 (12 527)*	10.756 (40 111)**
Gram-positive					
MRSA	9.125 (16 329)	11.374 (2151)*	10.554 (20 038)*	6.620 (10 866)*	8.864 (33 055)**
VRE	1.361 (2435)	2.866 (542)*	1.912 (3630)*	1.073 (1762)*	1.591 (5934)*
SP any NS	0.311 (556)	0.455 (86)**	0.222 (421)*	0.128 (210)*	0.192 (717)*

Abbreviations: AMR, antimicrobial resistance; ESBL, extended-spectrum β-lactamase; FQ, fluoroquinolone; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, nonsusceptible; Pip-Tazo, piperacillin-tazobactam; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SP, *Streptococcus pneumoniae*; VRE, vancomycin-resistant enterococci.

*$P < .001$ χ^2 test of significance compared to pre–SARS-CoV-2.

**$P < .01$ χ^2 test of significance compared to pre–SARS-CoV-2.

Table 4. Patient Level Multivariate Results for Severe Acute Respiratory Syndrome Coronavirus 2 Impact on Antimicrobial Resistance Rates Overall and by Community and Hospital Onset for Those With Gram-Negative/Gram-Positive Pathogens[a]

Characteristic	Overall Model (N = 514 519)		Community Onset (n = 410 125)		Hospital Onset (n = 104 394)	
	OR of Having AMR (95% CI)	*P* Value	OR of Having AMR (95% CI)	*P* Value	OR of Having AMR (95% CI)	*P* Value
SARS-CoV-2 time (ref: pre–SARS-CoV-2)						
SARS-CoV-2 period	0.942 (.929–.954)	<.001	0.939 (.925–.953)	<.001	0.982 (.902–1.068)	.667
SARS-CoV-2 status (ref: pre–SARS-CoV-2)						
Positive	1.156 (1.008–1.325)	.038	0.971 (.945–1.017)	.425	1.250 (1.168–1.364)	<.001
Negative	.946 (.930–.963)	<.001	0.947 (.929–.965)	.001	0.945 (.908–.984)	.005
Not tested	0.936 (.923–.950)	<.001	0.934 (.919–.950)	<.001	0.944 (.914–.976)	.001
Age	1.000 (.999–1.001)	.056	1.001 (.999–1.001)	.484	1.002 (1.002–1.003)	<.001
Male sex	1.128 (1.114–1.141)	<.001	1.159 (1.143–1.175)	<.001	1.026 (.999–1.053)	.056
Antibiotic use per day	1.034 (1.033–1.035)	<.001	1.029 (1.027–1.032)	<.001	1.038 (1.036–1.040)	<.001
GN/GP (ref: GN)						
GP	1.240 (1.223–1.257)	<.001	1.224 (1.205–1.244)	<.001	1.287 (1.250–1.326)	<.001
GN and GP	1.552 (1.512–1.593)	<.001	1.584 (1.537–1.633)	<.001	1.473 (1.399–1.551)	<.001
IET	2.142 (2.103–2.182)	<.001	2.199 (2.153–2.245)	<.001	1.922 (1.844–2.002)	<.001
Prior admission	1.513 (1.492–1.534)	<.001	1.514 (1.491–1.537)	<.001	1.501 (1.454–1.549)	<.001
Underlying conditions	1.069 (1.053–1.086)	<.001	1.064 (1.046–1.082)	<.001	1.100 (1.054–1.139)	<.001
Ventilated	1.000 (.971–1.029)	.972	1.018 (.977–1.061)	.385	1.007 (.965–1.051)	.737
ICU admission	1.038 (1.021–1.056)	<.001	1.071 (1.051–1.092)	<.001	1.055 (1.022–1.085)	.004

Abbreviations: AMR, antimicrobial resistance; CI, confidence interval; IET, inadequate empiric therapy; GN, gram-negative; GP, gram-positive; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Model comparing pre–SARS-CoV-2 versus SARS-CoV-2 periods run separately from model comparing SARS-CoV-2 testing status to pre–SARS-CoV-2. Covariates for the SARS-CoV-2 testing status models are shown; covariates did not significantly vary by model. All models also control for hospital demographics: urban/rural, teaching status, bed size, and region.

and SARS-CoV-2-negative patients in the HO setting ($P < .001$ for both) and in SARS-CoV-2–negative patients in the CO setting ($P < .001$). During the pandemic, all GN resistance types were significantly higher for SARS-CoV-2-positive and SARS-CoV-2-negative patients versus the prepandemic period ($P < .001$) except Pip-Tazo (not significant). All GN resistance types in the HO setting were significantly higher for SARS-CoV-2-positive and SARS-CoV-2-negative patients versus the prepandemic period ($P < .001$ for all), with HO carbapenem NS in SARS-CoV-2–positive patients showing the largest difference (1.317/1000 admissions in SARS-CoV-2–positive patients vs 0.292/1000 admissions prepandemic; $P < .001$).

Multivariate Results for Contributing Factors to AMR

In the multivariate analysis, patients admitted during the pandemic had significantly lower AMR compared with those admitted prepandemic overall and in the CO setting ($P < .001$; Table 4). However, SARS-CoV-2–positive patients were nearly 16% (odds ratio [OR], 1.156; $P = .038$) more likely to have AMR versus prepandemic patients overall, and 25% (OR, 1.250; $P < .001$) more likely in the HO setting. Duration of AU, the presence of GP or both GP/GN pathogens versus GN-only pathogens, and inadequate empiric therapy (IET) were significantly associated with higher AMR rates ($P < .001$ for all). Additionally, IET was associated with approximately twice the rate of AMR overall and in both CO and HO settings. Having a prior admission, any underlying condition, or ICU admission were also significantly associated with higher overall AMR rates.

Antimicrobial Use During Pre- and Postpandemic Periods

The percentage of admissions prescribed antibacterial therapy was significantly higher during the pandemic versus the prepandemic period (36.7% vs 35.0%; $P < .001$) and significantly higher in SARS-CoV-2–positive patients (57.8%) and SARS-CoV-2–negative patients (40.1%) (Table 2). This trend was similar in patients with a GN and/or GP pathogen in which AU ≥72 hours was significantly higher in SARS-CoV-2–positive (79.2%) and SARS-CoV-2–negative patients (72.1%) as compared to 68.9% prepandemic ($P < .001$ for both). Antibiotic use ≥72 hours in those with a negative culture or no culture collected was also significantly higher in SARS-CoV-2–positive (41.1%) and SARS-CoV-2–negative patients (21.0%) compared with 17.6% prepandemic ($P < .001$ for both).

In multivariate analyses, the risk for AMR increased with each day of antibacterial use in the CO and HO settings ($P < .001$ for all; Table 4). The daily OR for AMR during the entire study period was 1.034 ($P < .001$); thus, a patient receiving antibiotic therapy for 5 days would have a 17% greater risk for developing AMR (3.4% × 5 days). SARS-CoV-2–positive patients had significantly higher odds of AU versus the prepandemic patients in all models ($P < .001$) and were approximately twice as likely to have AU ≥24 hours (OR, 2.069) or ≥72 hours (OR, 2.352) if cultures were negative or not collected (Table 5). SARS-CoV-2–negative patients were also significantly more likely to have AU ≥24 hours and ≥72 hours with slightly higher odds of AU in all models except for AU in patients with GN/GP pathogens. All covariates were significant with the greatest risk of AU associated with having an underlying condition and being ventilated.

DISCUSSION

In this study of AMR in 5 518 666 hospitalizations, one of the first multicenter studies to evaluate the impact of the pandemic on AMR, we observed lower overall AMR rates during the pandemic period (35.4/1000 admissions) compared to the prepandemic period (34.7/1000 admissions). However, AMR rates were significantly higher among SARS-CoV-2–positive patients compared with prepandemic admissions, particularly in the HO setting and compared with those not tested for SARS-CoV-2. The increase in AMR observed during the pandemic period was driven largely by AMR among SARS-CoV-2–positive admissions in the HO setting, followed by SARS-CoV-2–negative admissions (9.9/1000 admissions). Most AMR phenotypes were lower across all admissions during the pandemic period except for ESBL+ and VRE, which were significantly higher during the pandemic. However, rates of carbapenem NS, ESBL+, FQ NS, MDR/pan-NS, MRSA, and VRE were significantly higher in both SARS-CoV-2-positive and SARS-CoV-2-negative patients compared to the prepandemic period and highest in SARS-CoV-2–positive patients overall and in the HO period.

Our findings were broadly consistent with those reported in a single-center study of AMR in bacterial infections in SARS-CoV-2–positive patients in Italy between March 2020 and January 2021 [24]. In this study of 1090 patients with symptomatic bacterial infections, no differences were observed between rates of AMR before and during the pandemic. Moreover, the percentage of microorganisms resistant to each of the 18 tested antibiotics was higher in SARS-CoV-2–positive versus SARS-CoV-2–negative isolates (12.0% vs 6.6%). The authors concluded that an increase in AMR may be occurring in SARS-CoV-2–positive patients, given the higher frequency of strains resistant to every tested antibiotic. In another study, the number and rate of AMR infections in Taiwan during the pandemic (January–June 2020) remained largely constant when compared with the prepandemic period (January–June 2019), despite a significant increase in the use of broad-spectrum antimicrobial agents [8]. Other studies have reported an increase in AMR resistance in regions with a high burden of severe or critical COVID-19 early in the pandemic, including in the US, Mexico, Wuhan, France, and Taiwan [4, 8, 13, 15, 16, 25].

As expected, multivariate analyses of factors potentially contributing to higher overall AMR rates included several modifiable (eg, higher rates and longer durations of AU, higher rates of IET) and nonmodifiable factors (eg, higher rates of GN/GP positivity). Our previous analyses have reported high rates of AU among SARS-CoV-2–positive patients without a documented bacterial infection, particularly early in the pandemic [18–20], and widespread use of antibiotics is known to contribute to the emergence of AMR. In the current study, SARS-CoV-2–positive patients had significantly higher AMR rates in all phenotypes evaluated. Data indicate that SARS-CoV-2–tested patients are more likely to receive antibiotics than untested patients, with the highest antibacterial use occurring in SARS-CoV-2–positive patients [19, 20], which

Table 5. Multivariate Results for Severe Acute Respiratory Syndrome Coronavirus 2 and Antibiotic Use for Those With and Without a Gram-Negative/Gram-Positive Pathogen

	Overall Model (N = 5 518 666)		With GN/GP Pathogen (n = 514 891)		With Negative GN/GP Pathogen or No Culture Collected[a] (n = 5 003 775)	
Characteristic	OR (95% CI) of AU ≥ 24 h	*P* Value	OR (95% CI) of AU ≥24 h	*P* Value	OR (95% CI) of AU ≥24 h	*P* Value
SARS-CoV-2 time (ref: pre–SARS-CoV-2)						
SARS-CoV-2 period[b]	1.035 (1.031–1.039)	<.001	0.981 (.964–.998)	.027	1.054 (1.049–1.058)	<.001
SARS-CoV-2 status (ref: pre–SARS-CoV-2)						
Positive	1.856 (1.837–1.874)	<.001	1.128 (1.106–1.150)	<.001	2.069 (2.047–2.091)	<.001
Negative	1.148 (1.143–1.154)	<.001	1.025 (.970–1.074)	.290	1.151 (1.146–1.156)	<.001
Not tested	0.833 (.830–.838)	<.001	0.813 (.795–.832)	<.001	0.863 (.859–.867)	<.001
Age	1.012 (1.011–1.012)	<.001	1.008 (1.008–1.009)	<.001	1.010 (1.010–1.010)	<.001
Male (ref: female)	1.018 (1.014–1.022)	<.001	1.623 (1.595–1.652)	<.001	1.052 (1.047–1.056)	<.001
Prior admission	1.320 (1.313–1.326)	<.001	1.045 (1.025–1.066)	<.001	1.264 (1.258–1.271)	<.001
Underlying conditions	2.215 (2.207–2.223)	<.001	1.454 (1.427–1.481)	<.001	1.999 (1.991–2.007)	<.001
Ventilated	4.271 (4.061–4.485)	<.001	3.267 (2.983–3.577)	<.001	4.167 (3.974–4.366)	<.001
ICU admission	1.848 (1.838–1.859)	<.001	1.130 (1.101–1.160)	<.001	1.773 (1.762–1.784)	<.001
	OR (95% CI) of AU ≥72 h	*P* Value	OR (95% CI) of AU ≥72 h	*P* Value	OR (95% CI) of AU ≥72 h	*P* Value
SARS-CoV-2 time (ref: pre–SARS-CoV-2)						
SARS-CoV-2 period	1.033 (1.028–1.038)	<.001	0.977 (.964–.989)	<.001	1.061 (1.055–1.066)	<.001
SARS-CoV-2 status (ref: pre–SARS-CoV-2)						
Positive	2.020 (1.999–2.041)	<.001	1.215 (1.173–1.259)	<.001	2.352 (2.326–2.379)	<.001
Negative	1.145 (1.139–1.151)	<.001	1.092 (1.076–1.108)	<.001	1.143 (1.136–1.149)	<.001
Not tested	0.811 (.806–.815)	<.001	0.787 (.774–.800)	<.001	0.847 (.841–.852)	<.001
Age	1.014 (1.013–1.014)	<.001	1.001 (1.000–1.001)	<.001	1.013 (1.012–1.013)	<.001
Male (ref: female)	1.040 (1.036–1.045)	<.001	1.564 (1.544–1.584)	<.001	1.059 (1.053–1.064)	<.001
Prior admission	1.457 (1.450–1.465)	<.001	1.226 (1.208–1.244)	<.001	1.425 (1.417–1.433)	<.001
Underlying conditions	2.593 (2.582–2.605)	<.001	1.797 (1.773–1.822)	<.001	2.418 (2.405–2.430)	<.001
Ventilated	4.311 (8.164–7.460)	<.001	4.154 (3.940–4.379)	<.001	4.412 (4.492–4.794)	<.001
ICU admission	1.995 (1.983–2.007)	<.001	1.817 (1.785–1.850)	<.001	1.916 (1.904–1.929)	<.001

Abbreviations: AU, antimicrobial use; CI, confidence interval; GN, gram-negative; GP, gram-positive; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Also includes admissions positive for a GN/GP pathogen not included as a pathogen of interest (1.16% of admissions).

[b]Model comparing pre–SARS-CoV-2 versus SARS-CoV-2 periods run separately from model comparing SARS-CoV-2 testing status to pre–SARS-CoV-2. Covariates for the SARS-CoV-2 testing status models are shown; covariates did not significantly vary by model. All models control for hospital demographics: urban/rural, teaching, bed size, and region.

may have contributed to higher AMR rates in SARS-CoV-2–positive patients in the HO setting.

Another notable finding from our analysis is the higher rate of IET in AMR admissions compared to all GN/GP-positive admissions, regardless of SARS-CoV-2 testing status. These findings were confirmed in a multivariate analysis indicating that higher IET rates were associated with higher AMR rates during the study period and that SARS-CoV-2–tested patients had significantly higher AU overall, and most notably among admissions with a negative or no culture result. Taken together, these findings offer an opportunity for improved antimicrobial stewardship interventions that may have been compromised during the pandemic and for careful attention to resource optimization of key antimicrobials during future outbreaks.

Adhering to optimal antimicrobial and diagnostic stewardship practices can be challenging, particularly under the complex circumstances of the COVID-19 pandemic [26]. Minimizing the development of AMR remains a significant challenge, given the widespread disruption of healthcare services, the unprecedented burden on healthcare workers, and a potential reduction in adherence to infection control practices. Addressing the potentially modifiable factors associated with the development of AMR is critical, including optimizing AU, specifically by addressing inadequate antibiotic prescriptions, particularly among SARS-CoV-2–positive patients, which remains the most effective strategy for tackling misuse of antimicrobials. To that point, strategically deployed diagnostic tests may need to be incorporated into stewardship programs to better inform definitive therapy earlier in the disease process and to reduce time patients receive unnecessarily broad antimicrobial coverage.

Our results expand the scope of previous studies of AMR during the COVID-19 pandemic by including multiple bacterial species and culture sites from many hospitals in diverse geographic regions, enabling our findings to be generalizable to admissions throughout the US.

Limitations of the study include the use of facility-reported results as the source of bacterial and SARS-CoV-2 results, the lack of a central laboratory, and the lack of a uniform method of AMR testing, all of which may have influenced the results. No case definition for COVID-19 disease was applied, suggesting that some included patients with SARS-CoV-2 could have been asymptomatic but admitted for other causes. While some patients with GN/GP pathogens may have lacked clinically significant infections, we used an established algorithm [23] designed to exclude admissions with colonizing microbes. Results for admissions positive for GN/GP pathogens other than the pathogens of interest (1.16%), which were included in the GN/GP-negative or no culture group, were consistent with those included in the general population. We also did not have information on infection prevention practices or workforce constraints that can influence AMR (eg, overcrowding, clinician workload, shortages of protective equipment). Certain geographic areas may have been underrepresented and larger hospitals in more urban areas may have been overrepresented, which may have influenced our results.

CONCLUSIONS

High rates of inadequate antimicrobial exposure among SARS-CoV-2–positive inpatients have prompted concerns about increased rates of AMR among hospitalized patients. While our data suggest no significant change in overall AMR rates during the pandemic compared to prepandemic periods, higher rates of AMR in SARS-CoV-2–positive HO infections have been observed. This increase in AMR in the HO setting appears to be driven, at least in part, by greater and longer durations of AU, use of IET, longer lengths of stay, and increased ICU admissions. To mitigate the potential long-term impact of COVID-19 on AMR, it is critical to continue to monitor AMR rates in later stages of the pandemic, implement effective AU, and provide strategies to control modifiable factors contributing to AMR, particularly in SARS-CoV-2–positive patients with HO infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. K. A. B., L. A. P., and P. A. M. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, and are shareholders in Merck & Co, Inc. L. A. P. was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, and a shareholder in Merck & Co, Inc, at the time of the study. K. C. Y., J. A. W., C. A., and V. G. are employees of Becton, Dickinson & Company, which was contracted by Merck to conduct the study. K. C. Y. and V. G. also own stock in Becton, Dickinson & Company. All other authors report no potential conflicts.

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