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Antibiotic prescribing trends in the US during the first 11 months of the COVID-19 pandemic

Karishma Desai ^a, Prachi Arora ^{b,*}, Saurabh Ghanekar ^c, Karin Johnson ^a, Ilene Harris ^a

^a IMPAQ International, 10420 Little Patuxent Parkway, Suite 300, Columbia, MD, 21044, USA

^b College of Pharmacy and Health Sciences, Butler University, 4600 Sunset Avenue, Indianapolis, IN, 46208, USA

^c Resultant (formerly KSM Consulting), 111 Monument Cir #202, Indianapolis, IN, 46204, USA

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ABSTRACT

Background: The study aims to compare antibiotic prescribing trends for U.S. COVID-19 patients, categorized by disease severity, and non-COVID-19 population with similar symptoms during 2019–2020 pandemic.

Methods: A retrospective observational cohort design using Symphony Health (January–November 2020). Sample population included about 13.3 million patients with at least one prescription claim ± 6 months from date of diagnosis of COVID-19 or COVID-19 like symptom. Cohorts were categorized based on diagnosis codes; COVID-19 positive cohorts 1 to 3 with severe, mild, and no symptoms, respectively and non-COVID-19 cohorts 4 and 5 with severe and mild symptoms, respectively. Descriptive statistics were calculated for demographic characteristics and acute antibiotic utilization (≤ 7 days) including total number of antibiotics, weekly rate of prescribing, and proportion of fills in three “appropriateness” categories (always appropriate, potentially appropriate, never appropriate).

Results: Three cohorts with a positive COVID-19 diagnosis code constituted a total of about 1.8 million patients (13.53%). About 22.79% of COVID-19 positive groups had severe symptoms, 24.43% had moderate symptoms and the majority, 52.78%, had no symptoms. In the analytical sample of 13 million, about 4.2 million antibiotic prescriptions were prescribed to 2.5 million patients (19%) within 7 days of the first diagnosis of either COVID-19 or COVID-19-like symptoms. Within the COVID-19 positive cohorts, about 11% received an antibiotic prescription, while the non-COVID-19 cohorts, about 19.70% received an antibiotic. Among patients with antibiotic prescriptions, about 37.01% were prescribed an antibiotic “appropriately”, 39.46% were prescribed a “potentially appropriate” antibiotic and about 22.64% received an “inappropriate” antibiotic. Among patients prescribed antibiotics, azithromycin was the most common, ranging from 21.80 to 44.80% for each cohort.

Conclusions: Although the overall proportion of COVID-19 patients receiving antibiotics was much lower than non-COVID-19 patients, the findings suggest use of antibiotics persisted despite guidelines against widespread use, particularly for patients with moderate and mild COVID-19 symptoms.

1. Introduction

The coronavirus pandemic (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) resulted in unprecedented turmoil not only in the general public but also within the medical community. With the rising death toll, the World Health Organization (WHO) declared COVID-19 the sixth public health emergency of international concern, following H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019).¹ As of 2021, estimates report over 584,000 deaths in United States of America and about 3.35 million deaths

worldwide.² Limited guidelines in the initial phase of the pandemic and lack of evidence-based treatments for COVID-19 left providers to use their best judgment to help their patients.

While researchers grappled to generate new evidence to aid clinical efforts, clinicians relied on early updates and previous knowledge of pandemics to fight back. Early case reports³ and studies⁴ suggested a potential positive role of antibiotics, alone or in combination with other treatment options, in the therapy of COVID-19 patients. Also, past viral pandemics suggested a simultaneous rise in secondary bacterial infections and increased antibiotic use.⁵ However, concerns around drug resistant bacterial strains have raised alarm for more cautious use of

* Corresponding author. College of Pharmacy and Health Sciences, Butler University, 4600 Sunset Ave, Indianapolis, IN, 46208, USA.

E-mail address: parora@butler.edu (P. Arora).

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antibiotics in general.⁶ As a result, while some opinions supported the use of antibiotics for COVID-19 positive patients, others were more cautious and against blanket guidelines to prescribing antibiotics.^{7–11} On May 27th 2020, World Health Organization published *Clinical management of COVID-19, interim guidance*, which supported the use of antibiotics for therapy or prophylaxis for severe COVID-19 patients but also discouraged antibiotic use for COVID-19 patients with mild or moderate symptoms unless clinical suspicion of bacterial infection existed.¹²

With long held concerns about drug resistant bacterial strains, and rising apprehensions of how a rapid acceleration of antibiotic use to try to manage COVID-19 could accelerate antimicrobial resistance of bacteria, it is essential to quantify the extent of antibiotic use as a fundamental step in understanding the repercussions. This study aims to compare antibiotic prescribing trends among COVID-19 patients categorized by their disease severity (severe vs. moderate vs. no symptoms) and to compare these trends to the counterpart non-COVID-19 patient population during the pandemic.

2. Materials and methods

2.1. Design

A retrospective observational cohort study design was used.

2.2. Data

Through COVID-19 Research Database, we used Symphony Health data which aggregates from a variety of sources, particularly insurance claims clearinghouses and pharmacies, with an estimated capture of 93% of the prescriptions dispensed in the US. An extract from this dataset was identified for the study duration from 1st January 2020 to 25th November 2020.

2.3. Sample

We used the U.S. Centers for Disease Control and Prevention (CDC)-recommended International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes for COVID-19 (U07.1 and B97.29) and the symptoms (severe and mild) associated with COVID-19^{13,14} to identify five mutually exclusive cohorts for this study. Cohort 1 comprised patients with COVID-19 diagnosis along with one or more severe symptoms within 7 days including viral pneumonia (J12.89), bronchitis (J20.8, J40), respiratory infection (J22, J98.8) or acute respiratory distress syndrome (J80). Cohort 2 constituted patients with COVID-19 diagnosis along with one or more mild symptoms within 7 days including cough (R05), shortness of breath (R06.02), chills with fever (R50.9), chills without fever or repeated shaking with chills (R68.83), muscle pain (R52), headache (R51), sore throat or acute pharyngitis (J02.9), new loss of either taste or smell (R43.9) and new loss of both taste or smell R43.8.¹³ Cohort 3 constituted patients with COVID-19 diagnosis but without any severe or mild symptoms. Cohort 4 constituted patients with no COVID-19 diagnosis but with at least one of the severe symptoms and Cohort 5 constituted patients with no diagnosis of COVID-19 but with at least one of the mild symptoms.

Index dates for cohorts 1, 2, and 3 were the first COVID-19 diagnosis date and index dates for non-COVID-19 cohorts 4 and 5 were the first symptom date in the Symphony database.

2.4. Inclusion-exclusion criteria

Patients were excluded if they didn't have at least one prescription claim 6 months before or after the index date, to ensure a 12-month continuous enrollment of the patients in the pharmacy claims data. With this criteria applied, about 3 million patients were excluded, leaving the analytical sample of about 13.3 million. The 2017 HEDIS list

of antibiotics, which contains all “antibiotics of concern” based on NCQA categorization,¹⁵ along with their appropriateness classification (described below), was matched to the prescription claims in Symphony data. Patients who had one or more prescription claims of the matched antibiotics within seven days of the index date were assessed in the study.

2.5. Outcomes

Antibiotic utilization variables were assessed for each cohort. The primary utilization outcomes consisted of total number of antibiotic prescriptions and weekly rate of antibiotic prescribing per 1000 population defined as the number of prescriptions per 1000 population.

Demographic variables of age and sex were evaluated for each cohort and for those who used antibiotics within each cohort.

In order to assess the need for antibiotics due to other conditions or complications, we used a previously developed methodology¹⁶ to classify the appropriateness of the antibiotic prescription by assessing the ICD-10-CM diagnosis codes within a 3-day time frame from the antibiotic fill date and categorized the prescription into mutually exclusive schemes: “always,” “sometimes,” or “never” appropriate. For this, we examined all diagnosis codes in claims during a look-back period that began seven days before antibiotic prescription fills and ended on the day fills occurred. Although earlier studies used a three day look back period, we deemed a seven day period more appropriate to account for more comprehensive assessment on the need for antibiotics due to other causes. We used a stepwise process to first identify if any of the ICD-10-CM codes were “appropriate”, if so the prescription was categorized as “appropriate”, followed by identifying ICD-10-CM that may be “sometimes” appropriate and “never” appropriate in the same manner. Additionally, we assessed the top 10 most frequently prescribed antibiotics and the top 10 diagnosis codes for people with antibiotic claims.

2.6. Statistical analysis

Descriptive statistics were conducted for the demographic characteristics and antibiotic utilization outcomes. The trends in the weekly rate of antibiotic prescribing per 1000 population, top 10 antibiotics prescribed and most common other diagnoses in all cohorts were presented in a graphical format. All the analysis was conducted using SAS statistical software version 9.4.

3. Results

As noted in [Table 1](#), the analytical sample size included about 13 million patients with a combined total of approximately 2.4 million antibiotic prescriptions. Three cohorts with a positive COVID-19 diagnosis code constituted a total of about 1.8 million patients (13.53% of all the cohorts). The patients were predominantly female with majority being 40–64 years old. About 22.79% of COVID-19 positive groups had severe symptoms, 24.43% had moderate symptoms and majority (52.77%) had no symptoms. Approximately 19% of the sample population received an antibiotic prescription within 7 days of the index date. Within the COVID-19 positive cohorts, overall about 11% received an antibiotic. Patients with severe symptoms had the highest proportion of antibiotic prescriptions (15.48% had an antibiotic prescription), closely followed by those with mild symptoms (13.08% had an antibiotic prescription). Among the non-COVID-19 cohorts, about 19.7% received an antibiotic (about 35% of non-COVID-19 with severe symptoms and about 18% of non-COVID-19 with mild symptoms). Patients with no symptoms had the lowest proportion of antibiotics prescriptions (7.52% had an antibiotic prescription).

Among the 2,450,181 patients with antibiotic prescription, about 37.01% were prescribed an antibiotic “appropriately”, 39.46% were prescribed a “potentially appropriate” antibiotic and about 22.64%

Table 1
Cohort characteristics.

	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Cohort 5	
	COVID-19 +ve				No COVID-19					
	N = 1,794,566				N = 11,464,524					
	(13.53%)				(92.17%)					
	w/severe symptoms		w/mild symptoms		w/no symptoms		w/severe symptoms		w/mild symptoms	
	N = 409047		N = 438481		N = 947038		N = 1054178		N = 10410346	
	(22.79%)		(24.43%)		(52.77%)		(9.20%)		(90.80%)	
	Sample	Sample w/ antibiotic Rx	Sample	Sample w/ antibiotic Rx	Sample	Sample w/ antibiotic Rx	Sample	Sample w/ antibiotic Rx	Sample	Sample w/ antibiotic Rx
N (%)	409047	63302 (15.48)	438481	57348 (13.08)	947038	71197 (7.52)	1054178	375680 (35.64)	10410346	1882654 (18.08)
Age [Mean (SD)]	57.78 (16.87)	53.95 (16.89)	46.71 (19.14)	47.04 (18.49)	45.18 (20.14)	46.12 (19.41)	47.54 (21.33)	46.83 (21.43)	44.61 (23.96)	38.45 (25.30)
Age categories	%	%	%	%	%	%	%	%	%	%
<20 years	1.83	2.42	8.61	7.82	11.61	9.85	13.1	14.26	20.75	29.03
20–39 years	14.18	18.47	28.41	26.9	29.88	28.34	21.53	20.81	20.29	19.94
40–64 years	42.34	47.71	41.9	45.46	37.41	40.93	39.14	39.92	32.19	29.64
65 and above	41.65	31.4	21.07	19.82	21.1	20.88	26.23	25.01	26.78	21.38
Sex	%	%	%	%	%	%	%	%	%	%
Female	50.28	52.9	58.79	59.88	58.82	60.19	60.4	60.48	57.61	58.79
Weekly Average Rate of prescribing (per 1000 patient population)		298.47		247.85		164.18		487.52		293.19
Appropriateness		%		%		%		%		%
Appropriate (A)		50.89		37.16		28.55		26.73		38.91
Sometimes (S)		17.76		27.84		26.35		48.22		39.29
Never (N)		28.66		32.44		37.54		24.74		21.16

Note: If the data on the cohort characteristics was missing, it was excluded from the analysis.

received an “inappropriate antibiotic” as described in the methods section. To explore indications for appropriate antibiotic prescribing, we assessed the most common diagnoses based on ICD-10 codes besides the diseases of the respiratory system (ICD 10, J00-J99) (Fig. 1). Some of the most common co-morbidities within the cohorts include hypertension, diabetes type-2, hyperlipidemia, chronic obstructive pulmonary disease, gastro-esophageal reflux and end stage renal disease. Antibiotics are almost always indicated for two of the most common diagnoses, urinary tract infection and pneumonia of unspecified organism.

As depicted in Fig. 2, the pattern of prescribing rates per 1000 patient population was distinct for each cohort with notable differences between the non-COVID-19 groups and COVID-19 positive groups. The trends (highs/lows) were comparable across all cohorts. Cohort 4 (Non-COVID-19 w/severe symptoms) averaging at 487 per 1000 per week had the highest prescribing rate among all cohorts through the study duration. Prescribing trends for all the cohorts followed a biphasic pattern, being higher from January through March followed by another peak during June 3rd - August 26th, and otherwise remaining steady

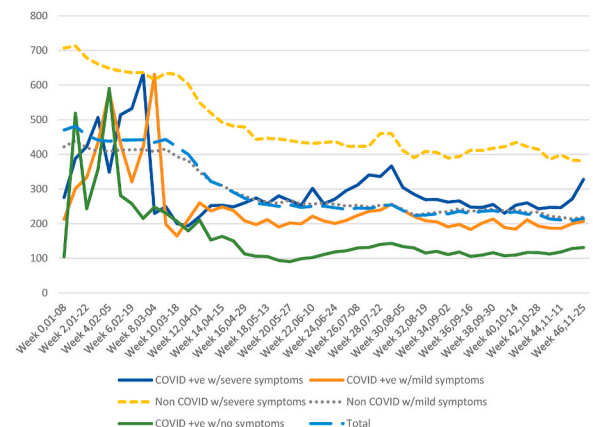


Fig. 2. Rate of prescribing antibiotics per 1000 people.

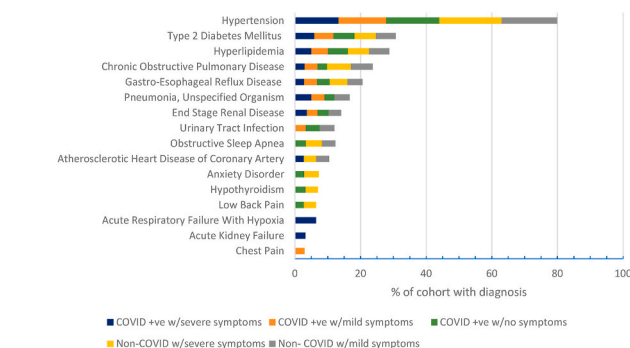


Fig. 1. Most Common Diagnoses among those with Antibiotic Prescriptions, by Cohort

Note: cohort percentages are non-additive.

throughout the year. Among the three COVID-19 positive cohorts, the prescribing rate was highest for Cohort 1 (positive COVID-19 w/severe symptoms) COVID-19 throughout the year and lowest for Cohort 3 (positive COVID-19 w/no symptoms). The initial erratic pattern for Cohorts 1–3 likely reflects the small numbers of patients in each cohort until mid-March.

Among patients prescribed antibiotics, azithromycin was most commonly prescribed antibiotic ranging from 21.8 to 44.8% of all antibiotic prescriptions for each cohort, with a total of about 900 k prescriptions. Other commonly prescribed antibiotics included amoxicillin-clavulanate potassium, doxycycline hyclate, amoxicillin, cefdinir and levofloxacin. Fig. 3 presents the proportion of each prescribed antibiotic within each cohort.

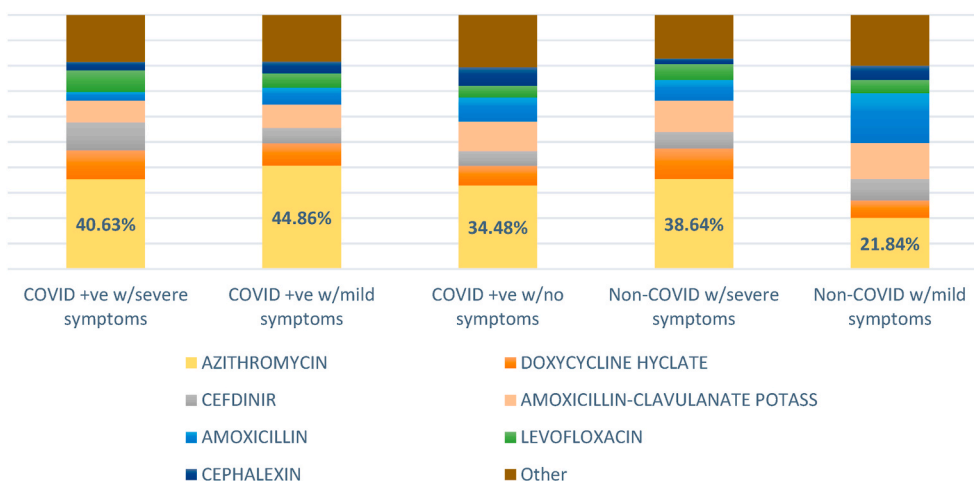


Fig. 3. Most commonly prescribed antibiotics, by Cohort.

4. Discussion

This study findings suggest the direction and notable fluctuations within the rate of antibiotic prescribing per 1000 people were comparable among COVID-19 positive and non-COVID-19 patient cohorts. A considerable number of antibiotics were prescribed to COVID-19 positive patients and the most severe cases had the highest rate of appropriate prescribing. The overall proportion of patients with COVID-19 receiving antibiotics was much lower in comparison to the non-COVID-19 cohorts with similar symptoms. Azithromycin, a broad spectrum macrolide antibiotic, commonly prescribed for respiratory infections,¹⁷ was the most prescribed antibiotic in all cohorts. About 28–38% of antibiotics prescribed for the COVID-19 positive cohorts and 21–25% in the non-COVID-19 cohorts were deemed to be not appropriate.

Early empirical studies suggest high use of antibiotics for COVID-19 patients, with about 56.6%–100% of hospitalized patients receiving an antibiotic.^{18,19} More recent reviews suggest similar proportions of about 74–75% of COVID-19 cases being prescribed antibiotics.^{20,21} Additionally, a few studies have examined co-occurrences of bacterial co-infections in patients with COVID-19 and found low rates of such infections.^{18,22} Our study corroborates the findings that a notable portion of COVID-19 patients received antibiotics, but our patient population is different than the other studies. Our dataset includes both outpatient antibiotic prescriptions and hospital medical claims information, hence capturing the severe and non-severe cases. Additionally, our study is unique in examining co-occurrences of other conditions and suggests there could be potential other infections that may have resulted in antibiotic use based on the appropriateness assessment. However, a quarter of the sample received unwarranted antibiotics. Hence, the use of antibiotics to this extent needs to be assessed with more granularity.

Our study did find a biphasic pattern in prescribing within the COVID-19 positive cohorts with erratic initial peaks based on the rate of prescription from January 2020 to March 2020, followed by a smaller peak from June 2020 to August 2020. The initial peaks in the antibiotic prescribing for the COVID-19 positive cohorts could have been due to limited knowledge of COVID-19 disease and more of a response to the sudden influx of patients with no known therapies. Additionally, the noted peaks may be a result of how COVID-19 was coded prior to the introduction of a new code discussed further under limitations. The second peak in the antibiotic prescriptions coincides with states easing stay-at-home orders by May 31st,²³ which potentially could have resulted in a spike in COVID-19 infections, along with other infections. A study by Gabriel et al. also noted a biphasic pattern during a shorter time frame,²⁴ from January 1st to April 30th within a single institution, corroborating the initial erratic peaks seen in our study.

Although the direction of prescribing rate trends appear to be

somewhat similar, the overall rates of prescribing were notably different with the non-COVID-19 cohort with severe symptoms maintaining the highest rate trend and the COVID-19 positive cohort with no symptoms maintaining the lowest rate trend. Based on the noted trends, there were short durations where substantial number of antibiotics were prescribed to COVID-19 patients and COVID-19 patients received a notable proportion of total antibiotics prescribed to all cohorts. These findings are similar to other studies within USA²⁵ and other countries noted similar patterns with spikes.²⁶ These small increases in prescribing rates could be again due to the unclear clinical guidelines with limited knowledge of the disease. Moreover, there was general disagreement about the clinical benefits of antibiotic use, particularly those of azithromycin. Our findings suggest azithromycin was the most prescribed antibiotic among all cohorts. Although azithromycin was initially a strong contender as a treatment option for COVID-19, clinical trials supporting its efficacy were still limited.^{27,28} Guidelines warned against the widespread use of antibiotics particularly for patients with moderate and mild COVID-19 symptoms.¹² That being said, the overall high number of prescriptions within the COVID-19 positive cohorts still warrant stronger efforts in implementing guidelines and translating them into clinical practice.

5. Limitations

The emergency ICD-10 code for COVID-19 was implemented on April 1st, 2020. To capture patients prior to April 1st, 2020, we used ICD-10 code B97.29 (Other coronavirus as the cause of diseases classified elsewhere), which may have resulted in additional patients not exclusive to the SARS-CoV-2/2019-nCoV virus. The B97.29 code does not distinguish the more than 30 varieties of coronaviruses, some of which are responsible for the common cold. However, due to the heightened need to uniquely identify COVID-19 before April 1, CDC recommended developing facility-specific coding guidelines that limit the assignment of code B97.29 to confirmed COVID-19 cases. Therefore, using the B97.29 codes to identify COVID-19 patients prior to April 1st 2020, was necessary for this study to access clinical practice when guidelines were limited. Our study duration partly overlaps with the flu season between December–March,²⁹ hence the numbers reported in our study for the COVID-19 cohorts might have been overestimated during this period. However, this should not affect the findings of our study which focuses on the antibiotic prescribing trends during the pandemic, especially since antibiotics are not approved as a treatment option for any coronavirus. This study used the ICD-10 codes from a past study by Chua et al. to assess the appropriateness of antibiotic prescription, however, ICD codes are often coded incorrectly in clinical practice which could affect the appropriateness measure of this study. Additionally, this study does not specifically assess appropriateness for

COVID-19-associated diagnosis codes with “sometimes appropriate” categorization (J02.9- pharyngitis, J22 unspecified acute lower respiratory infection) compared to appropriateness for co-occurring conditions. Additionally, some antibiotics could not be classified according to the appropriateness measure when patients had no diagnosis codes in the 7-day lookback period additionally, some of the newer antibiotics would not be classified since the study used to replicate the “appropriateness” variable does not include them. Future studies should account for prescribing appropriateness based on culture tests and other information to strengthen the assessment.

Despite these limitations, this study is the first study to analyze longitudinal prescribing trends and appropriateness of antibiotic use among COVID-19 positive patients and compare the use to non-COVID-19 patients. This is important in trying to understand how clinicians responded to conflicting information early in the pandemic and to what extent it affected prescribing patterns. Continued surveillance of antibiotic prescribing during the pandemic is needed to evaluate the long-term impacts of prescribing trends during COVID-19 and ramifications of growing antibiotic resistance strains. Additional antibiotic efforts should focus on COVID-19 patients with mild and no symptoms therapy to ensure reduced utilization among these subgroups.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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