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Original Article

One Health Bulletin

Are multiple courses of antibiotics a potential risk factor for COVID−19 infection and severity?

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ABSTRACT

Background: To determine the potential risk factor of COVID-19 severity and length of hospitalization, the association between multiple antibiotics administration and the risk of severe COVID-19.

Methods: A case-control study of 58 hospitalized COVID-19 patients (the case group) and 120 non-hospitalized home isolated COVID-19 patients (the control group) was conducted. Data were collected using hospital medical records and verbal questionnaires for the participants.

Results: Totally 89.2% of non-hospitalized mild COVID-19 patients received ⩽2 courses of antibiotics/year, while 36.0% of hospitalized patients received ⩾4 courses of antibiotics, 56.9% received 2-3 courses of antibiotics/year and only 6.9% of them were exposed to ⩽2 courses of antibiotics/year. our study emphasizes that the usage of 4 courses or higher per year was a significant risk factor for hospitalization [*OR*: 17.5; 95%*CI*(2.596-118.263); *P*=0.003], while the usage of ⩽2 courses was a preventive predictor for severity and hospitalization [*OR*: 0.072; 95%*CI*(0.006-0.900); *P*=0.041]. Furthermore, age was associated with 8.4% increase in the odds of severe COVID-19 [*OR*: 1.084; 95%*CI*(1.024-1.148), *P*=0.005], and females were 89.1% less likely to hospitalized than males [*OR*: 0.109; 95%*CI*(0.024-0.498); *P*= 0.004]. Our study shows that 70.4% of cases misused antibiotics and administered the antibiotics themselves without a physician's prescription. Around 50.0% of cases never completed the ideal duration of the course in contrast to controls, of which only 23.2% did not complete the ideal duration.

Conclusions: Our study shows that antibiotics misuse and overuse may be a potential risk factor for COVID-19 severity and hospitalization.

KEYWORDS: COVID-19 severity; Antibiotic frequent administration; Previous antibiotic exposure

1. Introduction

COVID-19 is a multisystem and multi-faceted infectious disease caused by the extreme acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the first reported case discovered in December 2019. Since then, the disease has spread globally, resulting in an unprecedented pandemic[1,2]. A systematic review and meta-analysis found that above 80.0% of COVID-19 cases suffered from mild to moderate symptoms, around 15.0% experienced severe symptoms that require hospitalization, and 5.0% called for ICU admission. The in-hospital mortality rate ranged from 23.4% to 33.0%[3-5]. Till July 2022, there were 572 239 451 confirmed cases of COVID-19, including 6 390 401 deaths, reported to WHO. Severe SARS-CoV-2 infection was reported in those with older age, chronic diseases,

Significance

The study sheds the light on the magnitude of COVID-19 severity regarding to the frequent and misusing of antibiotic administration. As reported in the preliminary studies, antibiotics misuse and overuse changed the microbial diversity and altered the immune response. Moreover, human intervention leads to the disturbance in the nature consequently, resulting in the emergence of the past, recent, and coming pandemics. All in all, the study emphasizes the association between antibiotic misuse and COVID-19 severity with an urgent call for a rational use of antibiotics in the future.

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How to cite this article: Shams MM, Hamdy EM, Abd-elsadek DF. Are multiple courses of antibiotics a potential risk factor for COVID-19 infection and severity? One Health Bull 2023; 3; 10. https://www.doi.org/10.4103/2773-0344.378589

Article history: Received 25 December 2022 Revision 10 January 2023 Accepted 30 May 2023 Available online 20 June 2023

male sex, and smokers[6,7]. Undoubtedly, immunity is the frontline and the guard against SARS-CoV-2 infection.

Antibiotics, considered as a double-edged weapon, are used to both prevent and cure bacterial infections[8,9]. In contrast to its valuable benefit in fighting a specific infection, it harms the microbiome. Recently, the widespread irrational consumption of antibiotic especially the broad-spectrum has been raised, which interrupts the performance of the microbiome and increases antibiotic resistance[10-12]. Furthermore, the previous studies confirm that antibiotics damage the ability of white blood cells to fight infections[13].

Our immune system plays a critical role in fighting infections including COVID-19. Several years ago, researchers confirmed the microbiome's role in developing innate and acquired immunity and *vice versa*[14]. A normal microbiome delimits the growth of harmful pathogens such as viruses, bacteria, and fungi[15,16]. Every time an antibiotic is administered, it cripples the microbiome[17], which interrupts the microbiome from performing its function in immunity, vitamin production, nutrition, and safeguarding from a harmful pathogen[18]. On the other side, host microbiota are greatly affected by intrinsic and environmental factors such as genetics, diet, antibiotics, and infection[19,20]. Microbiomes construct a good immune system that protects individual health, both gut-lung axes which have a fundamental role in the maturation of the immune system[21]. Latterly, several studies focus on the role of probiotics, prebiotics, and symbiotics in fighting SARS-CoV-2 infection and enhancement of immunity[22,23].

Antibiotic consumption changes the microbial community in the gut, lung, skin, and vagina, reduces the variation of the microbiome in the human body, and induces imbalance[24,25]. Moreover, dysbiosis is associated with COVID-19[26-28]. Additionally, previous studies confirmed the role of angiotensin-converting enzyme 2 in the adjustment of lung microbiota which was the entry of the COVID-19 virus into the human body[29,30]. As well, the recovery of the human microbiome after receiving an antibiotic course takes time from months to years[31].Thus, we hypothesized that multiple and frequent antibiotic administration in the era of antibiotic overuse would exacerbate COVID-19 severity and hospitalization. Especially, a study shows that the lung microbiome may impact COVID-19 susceptibility to infection[32].To note, the United States, Brazil, and India have more confirmed cases compared to other countries worldwide. In addition, in the United States, 35 000 deaths annually occur due to antibiotic resistance and overconsumption, While less antibiotic resistance has been shown in Finland, Denmark, and Sweden where a low level of COVID-19 pandemic infection occurs in them[33,34]. In a population infected with COVID-19, previous frequent and multiple antibiotic administration is a potential risk for COVID-19 severity and hospitalization. We conduct the study to determine the association between multiple antibiotics administration, and the risk of severe SARS-CoV-2 infection, and to predict one of the factors that may associate with COVID-19 hospitalization, depending on the fact that patients who receive multiple antibiotic courses are more likely to be infected with another infection[35-37].

2. Methodology

2.1. Study design

It's a case-control study conducted with the purpose to study the association between frequent antibiotic administration before the infection with COVID-19 and the susceptibility to COVID-19 severity. This study was carried out in the COVID-19 sorting clinics in El-Arish general hospital. Data were taken from the records of the included patients during the last four months of 2020 and the first two months of 2021 in a paper-based data collection form created especially. Data were collected from the COVID-19 hospital records and completed by verbal interview of those patients asking them about the frequency and rationale of antibiotic administration over the past years before the infection by COVID-19. We also asked the participants about the indication of antibiotic administration and if they had completed the ideal duration of antibiotic course.

2.1.1. Categorization

Five categories were summerized according to the administration of multiple antibiotic courses, including category 0($<$2 antibiotic courses administration the year before SARS-CoV-2 infection), category 1(2 antibiotic courses), category 2(3 antibiotic courses), category 3(4 antibiotic courses), and category 4($\geqslant$4 antibiotic courses), and assorted under three domains that are low intensity(category zero and one), intermediate(category two), and high intensity(category three and four).

The severity of COVID-19 was categorized as moderate (pneumonia without hypoxia), severe (pneumonia with hypoxia responding to oxygen therapy), and critical(pneumonia with hypoxia not responding to oxygen therapy and /or organ dysfunction).

2.1.2. Study date and duration

This study is retrospective research. The dependent variables were collected from the hospital medical records of patients who meet the criteria and sampling to be enrolled in the study starting from September 2020 to the end of February 2021. Verbal questionnaires were conducted about the exposure of patients during the past one year before their infection with COVID-19.

2.1.3. Population

Patients of the case group who were admitted to the inpatient wards, and ICU after the classification by COVID-19 sorting clinic into moderate, severe, and critical patients guided by COVID-19 protocol released from the Egyptian Ministry of Health and Population. Controls were selected from the same source population, patients admitted to the COVID-19 isolation clinic, and patients diagnosed with a mild SARS-CoV-2 infection.

2.1.4. Inclusion criteria and exclusion criteria

Patients aged ⩾18 years old, and patients with comorbidities and chronic disorders were included. The included patients should be alive and discharged from the hospital after SARS-CoV-2 infection and hospital admission. COVID-19 death cases and patients who were ⩽18 years old or pregnant, were excluded.

2.1.5. Sample size and type

Sampling was performed by systematic sampling technique from serials of the included patients. The sample size was estimated to be 55 cases, and we doubled the control to 120 patients. The total sample size was calculated to be 170 and we raised it to totally 178, including cases and control by ratio of 1:2. This sample was calculated based on the estimated *OR*=3, α=0.05, 95%*CI*, and power 0.8.

2.2. Statistical analysis

We used SPSS version 26.0 (Chicago, USA) and R software in our analysis. The *Chi*-square test or Fisher's Exact Test were used to investigate the association between categorical study factors. Mann-Whitney test was used to analyze the median difference in age between compared groups, while the parametric one-way ANOVA test was used to investigate the mean change in hospitalization length among related antibiotic usage variables groups. Simple frequency tables were used to assess an open-ended antibiotic indication question. We used a multivariate binary logistic regression to investigate the association between individual characteristics (demographic characteristics, existing chronic diseases, and previous antibiotic exposure factors) and hospitalization due to COVID-19 severity. Tables with 95%*CI* were used to illustrate adjusted odds ratios (aOR). Statistical significance was set as a *P*-value of less than 0.05. Categorical variables were described by frequency and percentage. For normally distributed continuous data, mean and SD were used to measure central tendency and dispersion, respectively. On the other side, skewed continuous data median, and IQR were used to measure central tendency and dispersion, respectively.

2.3.Ethical approval

The study was approved by the Egyptian MOHP Research Ethics Committee (REC). Approval Number (Com.No/DEC.No: 7-2023/35).

3. Results

3.1. Demographics and clinical characteristics

A total of 178 patients were incorporated into the study. Participants were divided into 58 cases and 120 controls. Cases that were hospitalized due to COVID-19 represented 26(44.8%) moderate cases, 24(41.4%) severe cases, and 8(13.8%) critical cases. Control group of 120 patients were home isolated for mild SARS-CoV-2 infection. As cases and controls were matched thus there were no significant differences between cases and control in age and comorbidities with the exception of sex as shown in Table 1 (*P*=0.006).

In our study, the median age of individuals was 41 years ranging from 19 to 83 years old with 91(51.1%) females and 87(48.9%) males. Less than half of the participants had at least one comorbidity (38.2%), hypertension was the most prevalent comorbidity in the total sample of 21.9% followed by diabetes 13.5% and heart conditions 6.7%. About 110(61.8%) of the total had no comorbidities and 32(55.2%) of the cases had no comorbidities at all.

3.2. Antibiotics exposure in the study population

In this study, previous antibiotic exposure per year was divided into five categories under three domains: Category 0 and1 (low intensity of ⩽2 antibiotics courses/year), Category 2, (intermediate intensity of 3 courses/year), Category 3 and 4 (high intensity of ⩾ 4 courses/year). Study results demonstrate that a high percentage

Table 1. Demographic and clinical characteristics of cases (hospitalized COVID-19 patients) and controls (home-isolated COVID-19 patients).

	Total (*n*=178)	Case patients (*n*=58)	Controls (*n*=120)	*P*[a]
Sex				0.006*
Female	91 (51.1%)	21 (36.2%)	70 (58.3%)	
Male	87 (48.9%)	37 (63.8%)	50 (41.7%)	
Age(years) median (min, max)	41 (19-83)	43.5 (22-83)	40 (19-82)	0.124†
Have comorbidities				
At least one comorbidity	68 (38.2%)	26 (44.8%)	42 (35.0%)	0.206*
Diabetes	24 (13.5%)	11 (19.0%)	13 (10.8%)	0.137*
Hypertension	39 (21.9%)	13 (22.4%)	26 (21.7%)	0.910*
Cardiac diseases	12 (6.7%)	3 (5.2%)	9 (7.5%)	0.753**
Immune deficiencies	3 (1.7%)	2 (3.4%)	1 (0.8%)	0.248**
Chronic lung diseases	11 (6.2%)	5 (8.6%)	6 (5.0%)	0.341**
Chronic kidney disease	2 (1.1%)	1 (1.7%)	1 (0.8%)	0.547**
Cerebrovascular disease	5 (2.8%)	2 (3.4%)	3 (2.5%)	0.661**
Disabilities	2 (1.1%)	1 (1.7%)	1 (0.8%)	0.547**
No comorbidities	110 (61.8%)	32 (55.2%)	78 (65%)	0.206

Data are expressed as *n*(%). [a] Differences between cases and controls; *Pearson *Chi*-square; †Mann-Whitney Test; ** Fisher's Exact Test; Bold font *P* denotes statistically significant associations.

64.2% of controls with mild SARS-CoV-2 infection used to administered ⩽2 antibiotic courses in the year before SARS-CoV-2 infection. On the other hand, only 6.9% of hospitalized COVID-19 cases were exposed to low-intensity antibiotic courses, while 20.7% and 15.5% of cases were exposed to ⩾4 courses antibiotics per year, respectively. The levels of antibiotic exposure intensity differed significantly between cases and controls ($P<0.001$). Totally 38.5% of the controls received no antibiotics during the year before SARS-CoV-2 infection while only 5.6% of the cases received no antibiotics. Another alarming finding is that 70.4% of cases took antibiotics by themselves without a physician's prescription(Table 2).

Table 2 also describes the attitude toward antibiotic usage regarding the prescription. Antibiotic self-administration and incomplete courses were higher in cases (70.4%, 50.0%) than in control (37.6%, 23.2%), and both variables differed significantly between compared groups ($P<0.001$).

For further analysis of the impact of antibiotic exposure, Figure 1 describes the association between the levels of antibiotic exposure during the year before infetion and the severity of COVID-19 cases ($P<0.001$). Antibiotic exposure ⩾4 courses was the highest in severe cases at 44.4% with 0% of mild COVID-19 controls. While for ⩽2 antibiotic courses administration per year, there weren't any critical cases, severe cases were at 2(2.5%) and it reached its maximum in controls of 77(95.1%).

Out of 118 study participants who reported previous antibiotic use, 112 (94.9%) individuals reported indications of use. Irrational antibiotic use for upper respiratory tract infection is the most frequent indication of antibiotic use in our sample which included common cold (51.7%), bronchitis (23.7%), followed by urinary tract infection (9.3%). (Figure 2).

Table 2. History of antibiotic exposure in the study population.

	Total (*n*=178)	Case patients (*n*=58)	Controls (*n*=120)	*P*[a]
Antibiotic exposure /year No. (%)				<0.001*
<2/year	81 (45.5%)	4(6.9%)	77 (64.2%)	
2/year	50 (28.1%)	20 (34.5%)	30 (25.0%)	
3/year	22 (12.4%)	13 (22.4%)	9 (7.5%)	
4/year	16 (9.0%)	12 (20.7%)	4 (3.3%)	
>4/year	9 (5.1%)	9 (15.5%)	0 (0%)	
Antibiotic prescription				<0.001**
No antibiotic use	45 (27.6%)	3 (5.6%)	42 (38.5%)	
Antibiotic without prescription	79 (48.5%)	38 (70.4%)	41 (37.6%)	
Antibiotic with prescription	32 (19.6%)	7 (13.0%)	25 (22.9%)	
Mixed antibiotic usage	7 (4.3%)	6 (11.1%)	1 (0.9%)	
Complete antibiotic course use				<0.001*
No antibiotics	45 (26.5%)	3 (5.2%)	42 (37.5%)	
Not completed course	55 (32.4%)	29 (50.0%)	26 (23.2%)	
completed course	45 (26.5%)	4 (6.9%)	41 (36.6%)	
Mixed antibiotic usage	25 (14.7%)	22 (37.9%)	3 (2.7%)	

[a]Differences between cases and controls; *Pearson *Chi*-square; **Fisher's Exact Test

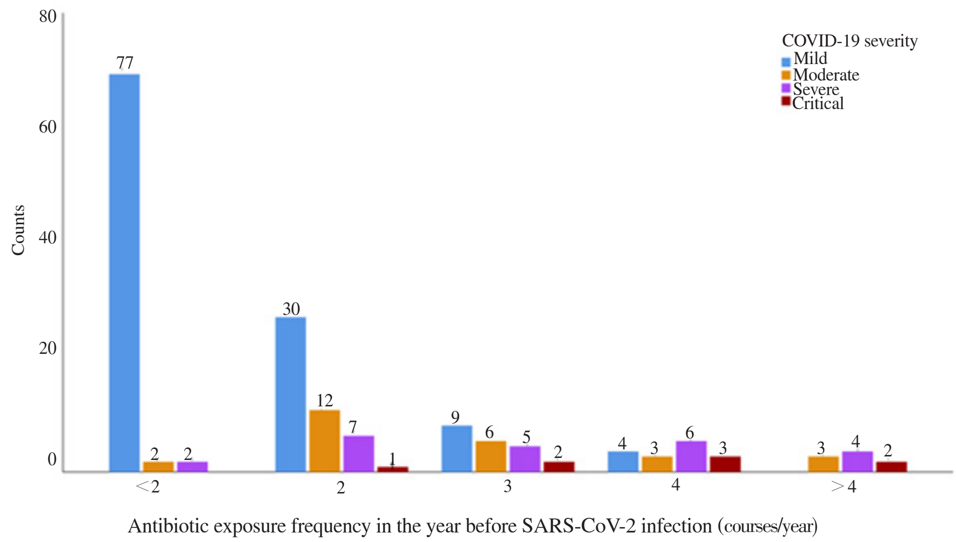

Figure 1. Antibiotic exposure intensity against COVID-19 severity

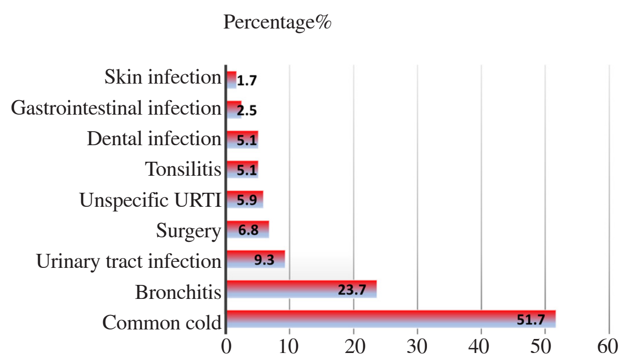

Figure 2. Self-reported indications of antibiotics use in the year before SARS-CoV-2 infection

Note: URTI, upper respiratory tract infection.

Figure 3 shows the association between different antibiotic usage behavior and hospitalization periods for COVID-19 hospitalized patients. Mean hospitalization periods were the longest in patients receiving ⩾4 antibiotic courses (14.8±7.7), further, the mean was 8.8±6.2 days and the difference was statistically insignificant (*P*=0.632) for patients with ⩽2 antibiotic courses per year. When comparing rational antibiotic use (prescribed antibiotic and completeness of courses), differences in the duration of hospital stay weren't statistically significant (*P*=0.554, *P*=0.465). Differences between groups tested by the one-way ANOVA test.

3.3. Multiple regression analysis

In the multivariable regression model, previous antibiotic exposure was significantly associated with increased odds of severe SARS-CoV-2 infection. After controlling for other variables, age and previous antibiotic exposure were the only predictors significantly associated with increased odds for severe COVID-19 in the multivariable regression model. Analysis indicated that completion of the antibiotic course duration was a significant protective factor against hospitalization for disease severity (*OR*: 0.015; *P*=0.001). The usage of ⩾4 courses was a significant risk factor for hospitalization (*OR*: 17.523; *P*=0.003), while the usage of ⩽2 courses was a preventive predictor (*OR*: 0.072; *P*=0.041). Each one-year increase in age was associated with an 8.4% increase in the odds of severe COVID-19 (*OR*: 1.084; *P*=0.005). Females were 89.1% less likely to hospitalized than males (*OR*: 0.109; *P*= 0.004)(Table 3).

4. Discussion

This retrospective case-control study was designed to assess the potential association between previous antibiotics frequent exposure and the risk of COVID-19 severity and hospitalization. The study results show that more than one-third (38.5%) of the non-hospitalized mild COVID-19 patients never received antibiotics while nearly all the hospitalized moderate, severe, and critical COVID-19 patients (94.5%) overused the antibiotics during the prior year of infection. Preliminary studies prove that antimicrobials adversely affect microbiota, and increase the load of resistant and pathogenic organisms[25,38,39]. In addition to inducing dysbiosis that alters the immune response against pathogens, it decreases microbial diversity and predisposes to other infections. Furthermore, antibiotics damage the ability of white blood cells to fight infection.

Table 3. Predictors of disease severity in COVID-19 patients by a binary logistic regression model.

	B	S.E.	Wald	Df	*P*	*OR*	95% *CI* for *OR*
Age	0.081	0.029	7.708	1	0.005*	1.084	1.024-1.148
Female gender	-2.214	0.774	8.177	1	0.004*	0.109	0.024-0.498
Diabetes mellitus	0.768	1.002	0.588	1	0.443	2.155	0.303-15.344
Hypertension	-0.414	0.870	0.227	1	0.634	0.661	0.120-3.639
Cardiac diseases	-0.063	1.107	0.003	1	0.955	0.939	0.107-8.219
Immunodeficiencies	1.751	2.504	0.489	1	0.484	5.760	0.043-779.473
Chronic lung disease	0.206	1.364	0.023	1	0.880	1.229	0.085-17.800
Chronic kidney disease	-0.357	1.734	0.042	1	0.837	0.700	0.023-20.936
Cerebrovascular Disease	1.457	1.424	1.047	1	0.306	4.294	0.264-69.968
Disabilities	-0.579	4.837	0.014	1	0.905	0.561	0.000-7344.290
Presence of at least one comorbidity	-0.579	1.052	0.303	1	0.582	0.560	0.071-4.407
Antibiotic prescription (ref= no antibiotic use)							
Self-use	2.795	1.732	2.604	1	0.107	16.366	0.549-487.826
Physician prescription	1.365	1.763	0.599	1	0.439	3.914	0.123-124.059
Both	1.474	1.943	0.575	1	0.448	4.365	0.097-196.725
Completed antibiotic course (ref=no antibiotic use)							
Not completed	-2.157	1.144	3.555	1	0.059	0.116	0.012-1.089
Completed course	-4.193	1.251	11.230	1	0.001*	0.015	0.001-0.175
Antibiotic exposure the year before SARS-CoV-2 infection (ref=2 courses/year)							
less than 2 courses	-2.625	1.285	4.170	1	0.041*	0.072	0.006-0.900
3 courses	0.804	0.794	1.025	1	0.311	2.235	0.471-10.600
4 courses or higher	2.863	0.974	8.640	1	0.003*	17.523	2.596-118.263

B: beta (regression coefficient); SE: standard error; df: degree for freedom; *OR*: odds ratio. **P* denotes statistically significant associations.

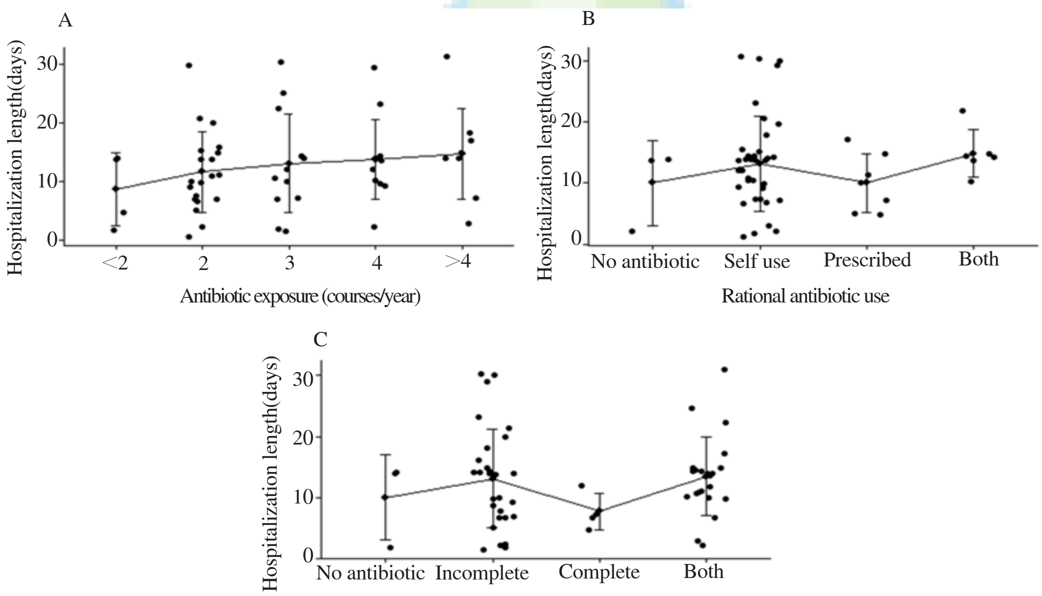

Figure 3. Hospitalization length of COVID-19 cases according to antibiotic exposure in the year before SARS-CoV-2 infection and antibiotic usage attitude. Differences between groups tested by the one-way ANOVA test. A: antibiotic exposure; B: rational antibiotic use; C: antibiotic course completion

Long-time and frequent antibiotic use curbs the strength of the immune system to fight infections like fungal and viral ones[13,40].

A high percentage (89.2%) of non-hospitalized mild COVID-19 patients were administered low-intensity antibiotics ⩽2 antibiotics per year. At the same time, none of them administered high-intensity antibiotics ⩾4 antibiotics/year, while about 36.0% of hospitalized patients received ⩾4, around 56.9% received 2-3 antibiotics/year and only 6.9% of them were exposed to ⩽2 antibiotics /year, indicating that the higher administration of antibiotic, the more severe the infection of COVID-19 and hospitalization would be. Research reveals that the human body takes time to restore the microbiome imbalance after the administration of each antimicrobial.

Some stated that it took six months for restoring, while others considered it took from months to years according to antibiotic class and spectrum[31,40-42].Thus, multiple and frequent antibiotic administration kills the immunity and delays the host's capability for restoration.

Correspondingly, our study emphasizes that the usage of four courses or higher was a significant risk factor for hospitalization (*OR*: 17.523; P=0.003), while the usage of less than two course was a preventive predictor for severity and hospitalization (*OR*: 0.072; P=0.041). There was statistically significance between the levels of antibiotic exposure of the year before SARS-CoV-2 infection and the severity of COVID-19 cases($P<0.001$). Patients who received low-intensity antibiotics were exposed to infection but with mild normal symptoms. Recently, antibiotic misuse has been rampant worldwide, consequently, resistance has emerged as a huge challenge for the world, which has conformed to the findings of our study that 70.4% of cases misuse antibiotics without a physician's prescription. They put themselves at risk of dysbiosis and weaken immunity and hospitalization. Studies show that dysbiosis was observed in hospitalized patients from the day of admission to recovery. Thus, the burden of pandemic infections and increased morbidity and hospitality is very likely to be associated with antibiotic misuse and overuse, especially in the last decades since antimicrobial resistance started and what is coming is obscure[43-45].

Moreover, 50.0% of cases never complete the ideal duration of the course in contrast to controls, of which only 23.2% did not complete the ideal duration. High-intensity antibiotic exposure was the highest in severe ICU admitted cases (44.4%) and the lowest in mild COVID controls (0%). There weren't any critical cases receiving low-intensity antibiotics while (89.2%) of mild controls received. In addition, around 94.9% of study participants reported the indication of antibiotic use. Upper respiratory tract infection was the most common cause of antibiotic administration presented as 86.4%, followed by urinary tract infection 9.3%. Our study shows that rational antibiotic use would not impact the duration of hospitalization. Mean hospitalization periods were the longest in patients $\geqslant$4 antibiotic courses (14.8±7.7), and for patients with $\leqslant$ 2 courses per year, the mean was 8.8±6.2 days but the difference was statistically insignificant(P=0.632). In a multi-regression analysis and controlling for potential confounders like age, sex, and comorbidities such as hypertension, diabetes mellitus, cancer, cardiovascular disease, and disabilities etc., only sex and age were statistically significant. Age was associated with an 8.4% increase in the odds of severe COVID-19 (*OR*: 1.084; P=0.005) females were 89.1% less likely to hospitalized than males (*OR*: 0.109; P=0.004), but other comorbidities saw no change. This might be because 61.8% of the sample never had comorbidities and only 38.2% had at least one comorbidity. Further, it is an unmatched case-control study with 55.2% of cases, and 65.0% of controls had no comorbidities.

5. Conclusions

In the era of the increased burden of antimicrobial resistance, overuse and misuse, we have a role in murdering our natural immunity and altering their ability to fight infections. We live in a community of harmful organisms that may cause several infections that immunity can fight and prevent its severity, but human interference is always insecure. Our study emphasizes the association between excessive antibiotic administration and the risk of COVID-19 severity and hospitalization. The usage of 4 courses or higher was a significant risk factor for hospitalization (*OR*: 17.523; P=0.003), while the usage of $\leqslant$2 courses was a preventive predictor for severity and hospitalization (*OR*: 0.072; P=0.041).

This study will draw more attention to using evidence studies concerning antibiotics issue involving samples representing the international population. Nevertheless, the weakness is the small sample size of the nature of the North Sinai governorate which contains a small population. Recall bias is a flaw for this type of study design, in which so some more data were planned to be studied but it was so difficult for the patient to recall such information. More studies need to be carried out to prob into the alarming issue of antibiotics misuse and overuse.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Acknowledgement

The authors would like to thank the study participants for their participation and cooperation.

Funding

The study received no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

Shams MM developed the Research idea ,coducted the literature review, contributed to the data analysis and interpretation, and wrote the full manuscript. Hamdy EM collected the epidemiological study data from the hospital and conducted the verbal questionnaire with patients. Abd-elsadek DF conducted the statistical analysis and data interpretation.

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