Low Rate of Bacterial Coinfections and Antibiotic Overprescribing During COVID-19 Pandemic: A Retrospective Study from Oman

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ABSTRACT

Objectives: The recommended treatment for COVID-19 includes antiviral drugs, corticosteroids, immunomodulatory drugs, low molecular weight heparin, as well as antibiotics. Although COVID-19 is a viral disease, many studies indicate that antibiotics are prescribed frequently, mainly to treat suspected bacterial coinfection. At the same time, the prevalence of bacterial coinfections during COVID-19 is rather low indicating the significant antibiotic overuse in these patients. It is well known that this can trigger antibiotic bacterial resistance, and once it emerges the reversal of resistance is a complex and long-lasting process. The aims of this study were to estimate the prevalence of bacterial coinfections during the COVID-19 and to analyze the antibiotic treatment justification during this pandemic in Oman. ***Methods***: This retrospective analysis was conducted using the Royal Hospital COVID-19 Registry Database. The study analyzed demographic and clinical characteristics, as well as laboratory parameters and antibiotic treatment of hospitalized patients. ***Results:*** During the study period, 584 patients were enrolled in the analysis. Coinfection was rare as it was confirmed in 0.9% of patients. Superinfections were present in 15.2% of patients. Gram-negative bacteria were isolated in 95 (69.9%) samples, gram-positive bacteria in 25 (18.4%) samples, while *Candida* spp. was found in 16 (11.8%) samples. On admission, empirical antibiotic treatment was started in 543 (93.0%) patients. ***Conclusions:*** During COVID-19, coinfections are rarely seen and the overuse of antibiotics is not justified. The incidence of superinfections is the same as in other patients in healthcare settings caused by the same resistant microorganisms, which implies the use of even more.

It has been more than two years since the world experienced the start of the COVID-19 pandemic caused by the newly identified coronavirus, SARS-CoV-2. Until the end of September 2022, more than 600 million people were infected and more than 6.5 million people died.[1] COVID-19 clinical presentation varies from asymptomatic infections to a severe life-threatening disease. The majority of symptomatic patients present with fever and cough, but those requiring hospital admissions, mostly due to dyspnea, usually have bilateral radiological chest infiltrates. Severe COVID-19 cases can present with acute respiratory distress syndrome, multiple organ dysfunction syndrome, and even death. So far published studies reported that the fatality rate of COVID-19 varies from 1.4–4.3%.[2]

Because of the fast and easy spread of the disease, as well as its severity, this pandemic not only dominates every aspect of the global healthcare systems but also it outstandingly influences every side of our lives including the global economy. These are several reasons why physicians and scientists are intensively struggling to find an efficient treatment to alleviate this disease, so far none of the used medications are undoubtedly effective. Throughout the world, the anti-SARS-CoV-2 vaccination campaign started at the beginning of 2021 and for the time being, it appears to be, together with public health measures, the only way to control the pandemic.[3] COVID-19 recommended treatment includes antiviral drugs, corticosteroids, immunomodulatory drugs, low molecular weight heparin, and antibiotics. Although

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COVID-19 is a viral disease, many studies indicate that antibiotics are prescribed frequently to treat suspected bacterial coinfection.[4,5] At the same time, the prevalence of bacterial coinfections during COVID-19 is low, indicating significant antibiotic overuse in these patients.[6] This can trigger antibiotic bacterial resistance, and once it emerges, the reversal of resistance is complex and long-lasting process.[7] During the study period, hospitalized COVID-19 patients in Oman were treated following the protocol that suggested the empirical use of antibiotics, only if bacterial pneumonia or sepsis were suspected. The antibiotic treatment was to be re-evaluated daily, and when there was no evidence of bacterial infection, the antibiotic treatment should be stopped.[8]

The aim of this study was to estimate the prevalence of bacterial coinfections in hospitalized COVID-19 patients and identify the most common microorganisms causing these infections. Our study also aimed to analyze the antibiotic treatment in these patients as the purpose of this research was to provide valuable data for antibiotic stewardship programs.

METHODS

This retrospective study was conducted using the Royal Hospital (RH) COVID-19 Registry Database. The RH in Muscat, Oman, is the main tertiary hospital designated nationally for the care of COVID-19 patients. The Registry contains demographic, clinical characteristics, laboratory parameters, medications, and clinical outcomes of all COVID-19 patients hospitalized in the RH.[9]

The study analyzed the patients' data consecutively admitted to adult wards for treatment between March and August 2020. As per the healthcare system in Oman, patients < 13 years of age are treated in pediatric wards so they were not enrolled in the study. Demographic (age and gender), clinical (symptoms at the admission, comorbidities, obesity defined as body mass index of ≥ 25 kg/m^2, type of admission, length of stay, and outcome), laboratory parameters at admission (white blood cell, absolute neutrophil and lymphocyte counts, lymphocyte/neutrophil ratio, C-reactive protein, and ferritin), and therapeutic (type and timing of antibiotic prescribed) data were collected from the Registry. The study was approved by the Royal Hospital Research and Ethics Committee (SRC#36/2020), and the informed consent was waived as it was a secondary analysis representing only the minimal risk for the patients.

Microbiology results were used for the infection diagnosis and classification. Positive blood (b/c), urine (u/c), and endotracheal aspirate cultures (ET/c) were considered to be possibly COVID-19 related while other positive cultures were considered unrelated. Staphylococci, other than *Staphylococcus aureus* and *Staphylococcus lugdunensis*, were considered clinically insignificant and were excluded from the analysis. Unspecified organisms (including positive microscopy findings with no culture result recorded) and results recorded as mixed growth or contaminant were excluded from all sample types. All *Corynebacterium* bacteria were excluded from blood cultures and *Candida* spp. was excluded from respiratory samples. Respiratory viruses other than SARS-CoV-2 were not routinely done since the microbiology laboratory prioritized SARS-CoV-2 over multiplex polymerase chain reaction testing during the pandemic. Clinically significant positive cultures that were sampled within the first 48 hours of admission were categorized as coinfection while those sampled after the first two days of the hospital stay were labeled as hospital-acquired infection (HAI).

Descriptive statistics was used to describe the data. Categorical variables were summarized as frequencies and percentages. Continuous variables were presented as means and SDs and the difference was analyzed using the Student's *t*-test. A statistically significant difference was considered if $p < 0.05$. The analysis was done using the Excel for Microsoft 365 program.

RESULTS

During the study period, a total of 584 patients were enrolled in the analysis. Out of them, 398 (68.2%) were males and 186 (31.8%) were females. The average mean±SD age of male patients was 51.0±15.2 years while females were older, and their mean age was 57.0±16.2 years, but this difference was not statistically significant. The baseline demographic and characteristics, the management, and outcome of enrolled patients are presented in Table 1. The most frequent comorbidities were hypertension and diabetes mellitus noted in 47.1% (n = 275) and 44.0% (n = 257) patients, respectively. Obesity was present in 17.1% (n = 100) of our patients.

Fever and shortness of breath were the commonest symptoms found in two-thirds of our

Table 1: Baseline characteristics, management, and outcome of COVID-19 patients.

Patients	n	%
Demographics		
Age, n (mean ± SD)	584 (52.9 ± 15.7)	100
Male	398 (51.0 ± 15.2)	68.2
Female	186 (57.0 ± 16.2)	31.8
Comorbidities		
Hypertension	275	47.1
Diabetes mellitus	257	44.0
Obesity	100	17.1
Chronic kidney disease	78	13.4
Chronic cardiac disease	73	12.5
Rheumatological disease	48	8.2
Chronic neurological disease	35	6.0
Chronic pulmonary disease	27	4.6
Current malignancy	22	3.8
Solid organ transplant	20	3.4
Chronic liver disease	18	3.1
Symptoms at the admission		
Fever	400	68.5
Shortness of breath	394	67.5
Cough	349	59.8
Diarrhea	141	24.1
Chest pain	120	20.5
Muscle aches	112	19.2
Sore throat	58	9.9
Ward type admission and treatment		
General ward	308	52.7
Intensive care unit	276	47.3
Invasive mechanical ventilation	218	37.3
Antibiotics on admission	543	93.0
Inpatients mortality	118	20.2
Length of stay, days	12.6 ± 13.8	
Laboratory parameters at the admission	**Reference value**	**Mean ± SD**
White blood cells	2.2–10 × 10^9/L	8.2 ± 5.8
Absolute neutrophil count	1–5 × 10^9/L	6.3 ± 4.5
Absolute lymphocyte count	1.2–4 × 10^9/L	1.6 ± 1.2
C-reactive protein	< 10 mg/L	119.0 ± 87.6
Ferritin	48–708 µg/L	1537.3 ± 3584.7

patients, 400 (68.5%) and 394 (67.5%), respectively. Less frequent, but also commonly noted, was cough in 59.8% (349) of patients.

At admission, patients mostly had lymphopenia but the inflammatory parameters were usually significantly elevated. The average C-reactive protein was 118.9±87.6 mg/L, while ferritin was 1537.3±3584.7 µg/L.

In our cohort, 308 (52.7%) patients were treated in general wards, 276 (47.3%) patients were treated in the intensive care unit (ICU), and out of this number, 218 (37.3%) were mechanically ventilated. Apart from the standard COVID-19 treatment, the empirical antibiotic treatment was started in 543 (93.0%) patients, meaning that at admission only 41 (7.0%) patients did not receive any antibiotics. The most frequently used antibiotic was ceftriaxone, which was prescribed in 367 (67.6%) patients. This was followed by piperacillin-tazobactam, vancomycin, meropenem, and amoxicillin-clavulanate used in 122 (22.5%), 27 (5.0%), 16 (2.9%), and 11 (2.0%) patients, respectively. The mean length of stay in the hospital was 12.6 days, and the overall inpatient mortality was 20.2% (n = 118). The mortality in the general ward was 5.5% (n = 17) while in the ICU it was 36.6% (n = 101).

Significant b/c, u/c, and ET/c results are presented in Table 2. Five patients had positive blood cultures during the first 48 hours of hospitalization so these infections are considered to be coinfections with SARS-CoV-2. In three coinfected patients, gram-positive bacteria were identified. Two of those patients had methicillin-sensitive *Staphylococcus aureus* bacteremia, and the third one had *Enterococcus faecalis* in the blood stream. One of the patients with gram-negative bacteremia had *Escherichia coli* and the other had *Aeromonas hydrophila*. Characteristics of the five patients with bacterial coinfection are presented in Table 3. These five infections indicate that the proportion of coinfections in COVID-19 is rare, and in our patients it was 0.9%.

Positive b/c, u/c, and ET/c sampled more than 48 hours after the admission were used to confirm superinfections. Sixty-five patients had positive blood cultures, 10 had positive u/c, and ET/c was positive in 61 patients. As some patients simultaneously had positive different sample cultures but with the same bacteria, the total number of patients with superinfections was 89 showing that 15.2% is the total proportion of HAI in our cohort.

Out of all positive cultures that were considered significant, gram-negative bacteria were isolated in 95 (69.9%) samples and gram-positive bacteria were isolated in 25 (18.4%) samples while *Candida* spp. was found in 16 (11.8%) samples. The most commonly isolated gram-positive bacteria were methicillin-resistant *Staphylococcus aureus* and *E. faecalis* detected in eight (5.9%) and 11 (8.1%)

Table 2: Bacteria and fungi causing infections in COVID-19 patients.

Microorganism	Coinfection, n	Superinfection, n			Total
	b/c	b/c	ET/c	u/c	n (%)
Gram-positive					
MSSA	2	3	1		4 (2.9)
MRSA		6	2		8 (5.9)
Enterococcus faecalis	1	7		4	11 (8.1)
Enterococcus faecium		2			2 (1.5)
Gram-negative					
Klebsiella pneumoniae		15	9	3	27 (19.9)
Klebsiella oxytoca		1			1 (0.7)
Pseudomonas aeruginosa		5	10	2	17 (12.5)
Escherichia coli	1	4	5	1	10 (7.4)
Enterobacter cloacae		1	6		7 (5.2)
Citrobacter koseri		1			1 (0.7)
Stenotrophomonas maltophilia		1	14		15 (11.0)
Burkholderia cepacia		1	9		10 (7.4)
Achromobacter spp.		1	1		2 (1.5)
Aeromonas hydrophila	1	1	1		2 (1.5)
Acinetobacter calcoaceticus			1		1 (0.7)
Serratia marcescens			2		2 (1.5)
Fungi					
Candida spp.		16			16 (11.8)
Total	5	65	61	10	136 (100)

b/c: blood culture; ET/c: endotracheal aspirate culture; u/c: urine culture; MSSA: methicillin-sensitive Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus.

Table 3: COVID-19 patients with bacterial coinfection.

No	Age	Gender	Comorbidity/condition	Microorganism isolated	Outcome
1.	70	Male	Hepatocellular carcinoma and palliative care	MSSA	Died
2.	27	Male	Diabetes mellitus and diabetic ketoacidosis	MSSA	Survived
3.	21	Male	Prosthetic infective endocarditis	*Enterococcus faecalis*	Died
4.	65	Male	Pyelonephritis and urosepsis	*Escherichia coli*	Survived
5.	61	Male	Cerebral palsy, bedridden, and recurrent hospitalizations	*Aeromonas hydrophila*	Died

MSSA: methicillin-sensitive Staphylococcus aureus.

samples, respectively. *Klebsiella pneumoniae* was found in 27 (19.9%) of the cultures followed by *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* which were isolated in 17 (12.5%) and 15 (11.0%) samples, respectively.

DISCUSSION

The result of this study points out that in COVID-19 patients, bacterial and fungal coinfections are rare, yet most patients receive empirical antibiotic treatment on admission. Two-thirds of our patients were middle-aged men with a mean age of 52.9±15.7 years. Although the female patients' mean age was 57.0±16.2 years, there was no statistically significant difference between these two groups. The most usual symptoms our patients had at admission were fever, cough, and shortness of breath, while hypertension and diabetes mellitus were the most often comorbidities present in our cohort. Almost half of our patients (276; 47.3%) were treated in the ICU, and out of this, 218 (79.0%) patients required respiratory support and invasive mechanical ventilation. Overall mortality was 20.2%, with significantly higher mortality in the ICU (36.6%). All this data show that the characteristics of our patients are like those in other published studies.[10]

Several studies on the coinfection and superinfection in COVID-19 have been published. Some of them are with small sample sizes, not all present data on the spectrum of bacteria causing the infections, and usually, these studies are not distinguishing coinfection from superinfection, nor colonization from infection.[11–13] A prospective multicenter study by Russell et al,[14] found that of almost 50 000 COVID-19 patients, coinfection was present in only 0.65% of patients. Surprisingly, superinfection also was rare and it was confirmed just in 1.56% of patients. Although our study was retrospective, which might bias the data, it also showed that coinfections were rare (0.9%). Contrary to Russell et al,[14] study superinfections in our patients were more frequently diagnosed (15.2%), and the most plausible explanation for this is the difference in the disease severity. Almost half of our patients were treated in the ICU, while in Russell's study, only 22% of patients were in the ICU indicating that the possibility of contracting a superinfection was significantly higher in our cohort. Higher rate of HAIs in more severe than in non-severe COVID-19 disease has been confirmed in other studies.[15]

In the Spanish study dealing with the incidence of coinfections and superinfections in 989 COVID-19 patients, bacterial and fungal infections were confirmed using *Streptococcus pneumoniae* urinary antigen test, sputum, bronchoalveolar lavage, blood, and urine cultures. Viral coinfection with *influenza* A and B, *parainfluenza, metapneumovirus*, and respiratory syncytial virus (RSV) was confirmed using multiplex polymerase chain reaction testing. Coinfection was confirmed in 3.1% patients, and the commonest bacteria isolated were *S. pneumoniae* and *S. aureus*. Six patients had viral coinfection caused by *influenza* A, B, or RSV. Some patients had more than one type of bacteria isolated, and some patients with viral coinfection also had bacteria in the culture.[16] Similar rate of coinfections (3.2%) was found among 643 COVID-19 patients in a retrospective study in a UK secondary-care setting.[17] Bacterial or fungal infections were confirmed with cultures done according to the standard microbiology procedure, but all isolate identification was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. At the same time, *S. pneumoniae* and Legionella urine antigen tests, GeneXpert for influenza A/B, and RSV were done. *S. aureus* and *S. pneumoniae* were the most common gram-positive bacteria isolated, but various gram-negative bacteria were isolated too. The relatively high bacterial coinfection rate reported by the authors is probably related to their decision to consider a co-infection the one that occurred during the first five days of admission. None of the urine antigen tests were positive, and no viral coinfections were confirmed too.[17] Although the number of coinfections reported in these two studies was small, the reported coinfection rate was higher than in our study. Most probably it was overestimated, and the possible explanation for this might be that the Spanish study did not distinguish colonization from infection, and the UK study included those infections occurring even 48 hours after the admission, which should be considered as super-infections or HAI.[18] In their review and meta-analysis, Langford et al,[19] found that coinfections were confirmed in 3.5% (95% CI: 0.4–6.7%) of COVID-19 patients, and superinfections were presented in 14.3% (95% CI: 9.6–18.9%) of patients.[19]

Superinfections were confirmed in 89 (15.2%) patients. From the type of positive culture, it can be concluded that the most common infections in our cohort were bacteremia/fungemia, respiratory infections (ventilator-associated or hospital-acquired pneumonia, and tracheobronchitis), and urinary tract infection. All the isolated microorganisms have been associated with HAIs and many of them are from the *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. group of bacteria.[20] It is well known that 5–15% of hospitalized patients acquire HAI, and this proportion in the ICU settings can rise up to 37%.[16] The type of microorganisms causing superinfections in COVID-19 patients as well as the proportion of infected patients support the conclusion that superinfections in these patients are typical HAIs and that they should be managed accordingly.

Although COVID-19 is a viral infection and guidelines recommend rational use of antibiotics, clinicians overuse antimicrobials. The initial justification for the wide use was based on three different postulates. The first postulate is the previous experience with influenza caused by different influenza viruses, and the experience with other coronavirus respiratory diseases such as SARS and MERS. In these viral pneumonias, bacterial infection was present as coinfection or superinfection in 11–35% of cases so similar rate of bacterial infections was expected in COVID-19 too. The other potential reason for antibiotic use in viral diseases is the in vitro antiviral activity of certain antibiotics such as azithromycin.[21] The usual differential diagnosis process is the third reason for the antibiotic treatment of COVID-19 patients. The majority of COVID-19 patients admitted to the hospital are very sick and sometimes it is extremely difficult to distinguish if the illness is of viral or bacterial origin. Clinicians in their daily work are using the usual inflammatory markers to distinguish between the two etiologies, yet these parameters sometimes are not helpful in COVID-19.[22]

One of the limitations of our study is that no microbiological diagnostic tests were done to detect possible coinfection caused by atypical bacteria or viruses other than SARS-CoV-2. Although this might have affected the study result, other published studies confirm that infections with these organisms are rather rare supporting the general finding of our study of low coinfection rates. The retrospective data collection is one of the study's limitations. Some data were missing or incorrectly entered which influenced the proper analysis. Also, this prevented more detailed analysis of starting the empirical antibiotic criteria. Another study limitation is that the viral and atypical bacterial etiology confirmation was not done giving the possibility that some coinfections were not detected.

CONCLUSION

During the first two days since the COVID-19 patient admission, coinfections are rarely seen and the overuse of antibiotics is not justified. At the same time, the incidence of HAIs is the same as in any other patient in healthcare settings and caused by the same resistant microorganisms, which implies the use of even more antibiotics. This antibiotic overuse is a huge pressure that will induce the spread of bacterial resistance. Immediate antibiotic stewardship activities are needed to control antibiotic overprescribing and the emergence of resistant microorganisms. As the antibiotic stewardship activities were already implemented during the COVID-19 pandemic course, it would be advisable to analyze the antibiotic consumption during later pandemic phases which could indicate the most effective antibiotic stewardship activities.

Disclosure
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