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ORIGINAL RESEARCH

Coinfections in Patients Hospitalized with COVID-19: A Descriptive Study from the United Arab Emirates

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Purpose: Microbial coinfections in COVID-19 patients carry a risk of poor outcomes. This study aimed to characterize the clinical and microbiological profiles of coinfections in patients with COVID-19.

Methods: A retrospective review of the clinical and laboratory records of COVID-19 patients with laboratory-confirmed infections with bacteria, fungi, and viruses was conducted. Only adult COVID-19 patients hospitalized at participating health-care facilities between February 1 and July 31, 2020 were included. Data were collected from the centralized electronic system of Dubai Health Authority hospitals and Sheikh Khalifa General Hospital Umm Al Quwain.

Results: Of 29,802 patients hospitalized with COVID-19, 392 (1.3%) had laboratory-confirmed coinfections. The mean age of patients with coinfections was 49.3±12.5 years, and a majority were male (n=330 of 392, 84.2%). Mean interval to commencement of empirical antibiotics was 1.2±3.6 days postadmission, with ceftriaxone, azithromycin, and piperacillin–tazobactam the most commonly used. Median interval between admission and first positive culture (mostly from blood, endotracheal aspirates, and urine specimens) was 15 (IQR 8–25) days. *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* were predominant in first positive cultures, with increased occurrence of *Stenotrophomonas maltophilia*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter* baumannii, *Candida auris*, and *Candida parapsilosis* in subsequent cultures. The top three Gram-positive organisms were *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Staphylococcus aureus*. There was variability in levels of sensitivity to antibiotics and isolates harboring *mecA*, *ESBL*, *AmpC*, and carbapenemase-resistance genes were prevalent. A total of 130 (33.2%) patients died, predominantly those in the intensive-care unit undergoing mechanical ventilation or extracorporeal membrane oxygenation.

Conclusion: Despite the low occurrence of coinfections among patients with COVID-19 in our setting, clinical outcomes remained poor. Predominance of Gram-negative pathogens, emergence of *Candida* species, and prevalence of isolates harboring drug-resistance genes are of concern.

Keywords: SARS-CoV2, microbial coinfections, clinical outcomes, *Pseudomonas*, *Candida*

Introduction

COVID-19 is a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which was first identified in Wuhan, China in December 2019. The outbreak was declared a pandemic by the World Health Organization on March 11, 2020. Although a majority of patients with COVID-19 have mild symptoms, some experience a severe clinical course characterized by

multisystemic and life-threatening manifestations, with pneumonia and acute respiratory distress as prominent features.[1,2] The presence of comorbidities, such as hypertension, diabetes, and obesity, as well as old age, have been linked with increased COVID-19 severity and mortality.[1]

Microbial coinfections have been postulated to negatively impact host immunofunction and response to antibacterial therapy, which may contribute to poor patient outcomes.[3] Indeed, bacterial coinfection in viral pneumonia is a recognized predictor of mortality.[4,5] During previous coronavirus outbreaks (SARS-CoV and Middle East respiratory syndrome coronavirus) coinfections with respiratory pathogens, including influenza, human metapneumovirus, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*, were reported.[3,6–8] In the ongoing COVID-19 pandemic, viral, bacterial, and fungal coinfections have been reported among patients with COVID-19.[9,10] In a systematic review evaluating the burden of coinfections in patients with COVID-19, it was shown that 7% of patients hospitalized with COVID-19 had bacterial coinfections, increasing to 14% in studies that included only intensive-care unit (ICU) patients.[10] In addition, bacterial coinfection was a predictor of mortality.[10]

Frequent use of empirical antibiotics in patients hospitalized with COVID-19 poses a risk of selection for antibiotic-resistant strains.[11] Additionally, coinfections with multidrug-resistant pathogens could contribute to prolonged duration of hospitalization, increased treatment costs, and poor clinical outcomes in patients with COVID-19. Current reports on coinfections in COVID-19 patients do not provide the full microbiological profiles of the pathogens identified.[9,10] Therefore, to address this gap in the literature, this study was carried out to describe the prevalence and outcomes of coinfections in patients with COVID-19 and characterize the spectrum of causative agents and their antimicrobial-susceptibility profiles.

Methods
Study Design and Sites
This was a retrospective-cohort observational study of adult patients hospitalized with confirmed COVID-19 infections at participating centers between February 1 and July 31, 2020. A positive COVID-19 case was defined as person with a confirmed positive result on a nasopharyngeal swab tested using RT-PCR testing for SARS-CoV2. The study was carried out in the Dubai and Umm Al Quwain emirates of the United Arab Emirates.

Data were collected from the centralized electronic system that covers all Dubai Health Authority hospitals and from Sheikh Khalifa General Hospital, which is the main COVID-19 facility in Umm Al Quwain. Only adult patients hospitalized with COVID-19 were included, and patients under the age of 18 years and pregnant women were excluded. Ethics approval for the study was obtained from the Dubai Scientific Research Ethics Committee (DSREC-06/2020_24) and Emirates Institutional Review Board for COVID-19 Research (DOH/CVDC/2020/1359). A waiver for patient consent was given by the ethics committee, as this was a retrospective analysis of data already on the electronic medical records. Patient-data confidentiality was maintained, and the study was carried out in compliance with the Declaration of Helsinki.

Data Collection
Clinical and microbiological data of eligible patients were extracted from medical and laboratory electronic systems. These included underlying comorbidities, duration of hospitalization, COVID-19–specific and other anti-infective therapy, clinical progression, including ICU admission and ventilation, and outcomes. From the microbiology-laboratory records, we obtained information on specimen types and microbiological investigation carried out, pathogens identified, antimicrobial-susceptibility profiles, and resistance genes. Positive cultures from specimens obtained for screening purposes (eg, methicillin-resistant *Staphylococcus aureus* screening) or those reported as contaminants (eg, from blood or urine cultures) were excluded. Microbiological investigations and reporting in the diagnostic laboratories were carried out using standard protocols in keeping with Clinical and Laboratory Standards Institute guidelines.[12] BioFire FilmArray (BioMérieux, Marcy l'Etoile, France) respiratory-panel and pneumonia-panel assays were carried out in accordance with manufacturer protocols.

Statistical Analysis
Data were entered and analysed using SPSS 24. Descriptive statistics for categorical variables are presented as numbers and percentages and continuous variables as means ± SD or medians and IQRs.

Results
During the study period, 29,802 patients with COVID-19 were hospitalized across participating centers. We identified 392 patients (1.3%) with laboratory-confirmed coinfections.

The mean age of patients with coinfections was 49.3±12.5 years, and a majority were male (330 of 392, 84.2%). The predominant comorbidities identified were diabetes (117 of 392, 29.8%), hypertension (95 of 392, 24.2%), and asthma and cardiac disease (18 of 392, 4.6% each). A majority of patients received lopinavir–ritonavir (n=153) and favipiravir (n=111) as initial drugs for SARS-CoV2, while 68 received hydroxychloroquine. Of the 392 patients with coinfections, 130 (33.2%) died, predominantly those who required ICU care, mechanical ventilation, or extracorporeal membrane oxygenation (Table 1). The demographic and clinical profile of patients with coinfections is shown in Table 1.

The median duration of hospitalization was 21 (IQR 12–37) days. Mean interval between hospitalization and commencement of antibiotics was 1.2±3.6 days. The most common antibiotics administered were ceftriaxone (n=136), azithromycin (n=74), and piperacillin–tazobactam (n=41). The BioFire FilmArray respiratory panel using nasopharyngeal swab specimens was carried out on admission for 81 patients, of whom only two were positive (one each for rhinovirus and parainfluenza virus). The pneumonia panel was carried out using lower respiratory tract specimens for 48 patients, and this was done within 96 hours of admission

for all patients, except two, who had the test done on days 13 and 14 of hospitalization. A majority of the tested patients (34 of 48, 62.5%) were positive, with the predominant organism being *Haemophilus influenzae*, followed by *S. aureus*. Fifteen patients had single-organism infections, predominantly *H. influenzae* (n=12, Figure 1) while eight of the 13 patients with two-organism infections and all six patients with three-organism infections harbored *H. influenzae* (Table 2).

All 392 patients had laboratory-confirmed coinfections based on positive microbiological cultures. A majority (221 of 392) had single microbiological culture results. There were 171 patients considered to have superinfections, as they had more than one positive-culture result (range two to six) based on isolates from different body sites during their hospitalization. Median interval between admission and first positive-culture report was 15 (IQR 8–25) days. A majority of microbial cultures were identified from blood and central-line cultures, followed by endotracheal aspirates and urine (Figure 2). When we looked specifically at first positive-culture results, the most commonly identified organisms were Gram-negative pathogens, namely *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. Among the Gram-positive organisms, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *S. aureus* were predominant, while *Candida albicans* and *Candida tropicalis* were the most common fungal pathogens. Figure 3A shows the top 20 microorganisms identified from first positive cultures (Supplementary Figure 1 shows all organisms identified).
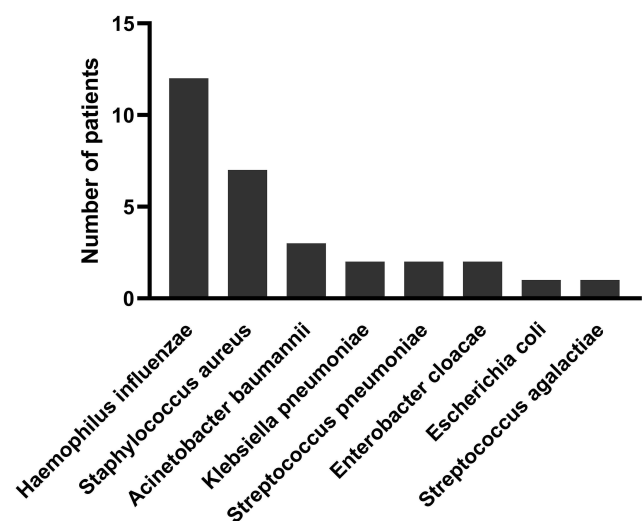
Table 1 Demographic and clinical profile of COVID-19 patients with coinfections

Age (years), mean ± SD	49.3±12.5	
Sex, n (%)	Male	330 (84.2%)
	Female	62 (15.8%)
Comorbidities, (%)		
	Diabetes	129 (33%)
	Hypertension	95 (24.2%)
	Cardiac disease	18 (4.6%)
	Asthma	18 (4.6%)
	Chronic renal disease	16 (4.1%)
	Neurological disease	9 (2.3%)
	Malignancy	7 (1.8%)
	Chronic respiratory disease	5 (1.3%)
Outcome, n (%)	Died	130 (33.2%)
Type of care	Total, n (%)	Died, n (%)
ICU critical care	219 (55.8%)	113 (51.6%)
Mechanical ventilation	201 (51.3%)	111 (55.2%)
Extracorporeal membrane oxygenation	14 (3.6%)	10 (71.4%)

Figure 1 Distribution of respiratory pathogens among patients with a single organism detected on pneumonia panel.

Table 2 Respiratory pathogens detected in patients positive for more than one organism on the pneumonia panel

Patients, n	
Two organisms	
Haemophilus influenzae, Staphylococcus aureus/methicillin resistant Staphylococcus aureus	4
Haemophilus influenzae, Klebsiella pneumoniae	2
Haemophilus influenzae, Pseudomonas aeruginosa	1
Haemophilus influenzae, human rhinovirus/enterovirus	1
Haemophilus influenzae, Acinetobacter baumannii	1
Staphylococcus aureus, Enterobacter cloacae complex	1
Acinetobacter baumannii, Enterobacter cloacae complex	1
Escherichia coli, Klebsiella aerogenes	1
Streptococcus agalactiae, adenovirus	1
Three organisms	
Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae	2
Haemophilus influenzae, Staphylococcus aureus, Streptococcus agalactiae	1
Haemophilus influenzae, Staphylococcus aureus, Acinetobacter calcoaceticus–baumannii complex	1
Haemophilus influenzae, Pseudomonas aeruginosa, Klebsiella pneumoniae	1
Haemophilus influenzae, Acinetobacter calcoaceticus–baumannii complex, *Enterobacter cloacae* complex	1

However, when all available positive microbial cultures from the entire period of hospitalization were considered, increased prevalence was found for *Stenotrophomonas*

maltophilia, methicillin-resistant *S. aureus*, and *Acinetobacter* baumannii, and the emergence of *Candida auris* and *Candida parapsilosis* among the top 20 organisms was observed (Figure 3B). A summary of the distribution of sensitivity to antibiotics tested is shown in Table 3. There was variability in sensitivity for antibiotics, with a trend toward resistance. For the commonly administered antibiotics, susceptibility testing was done infrequently for ceftriaxone (n=8), and only 40% of the 75 isolates tested for piperacillin–tazobactam were sensitive. There were 41 *S. aureus* isolates positive for the *mecA* gene while 65 *E. coli* and 39 *K. pneumoniae* isolates were identified as *ESBL* producers. There were 33 *AmpC*-producer isolates, comprised of *E. coli* (n=11), *Serratia* spp. (n=9), *Enterobacter cloacae* (n=8), *Klebsiella* spp. (n=4), and *Morganella morganii* (n=1). A majority of the 52 carbapenem-resistant isolates identified were *P. aeruginosa* (n=48), and the rest were *K. pneumoniae* (n=4).

Discussion

Bacterial coinfections occurring in patients with viral lower respiratory tract infections are frequently associated with significant morbidity and mortality. Based on this premise and experience from previous influenza pandemics, the use of empirical antibiotics in SARS-CoV2–infected patients was instituted in the ongoing COVID-19 pandemic.[13] However, the pattern of coinfections in
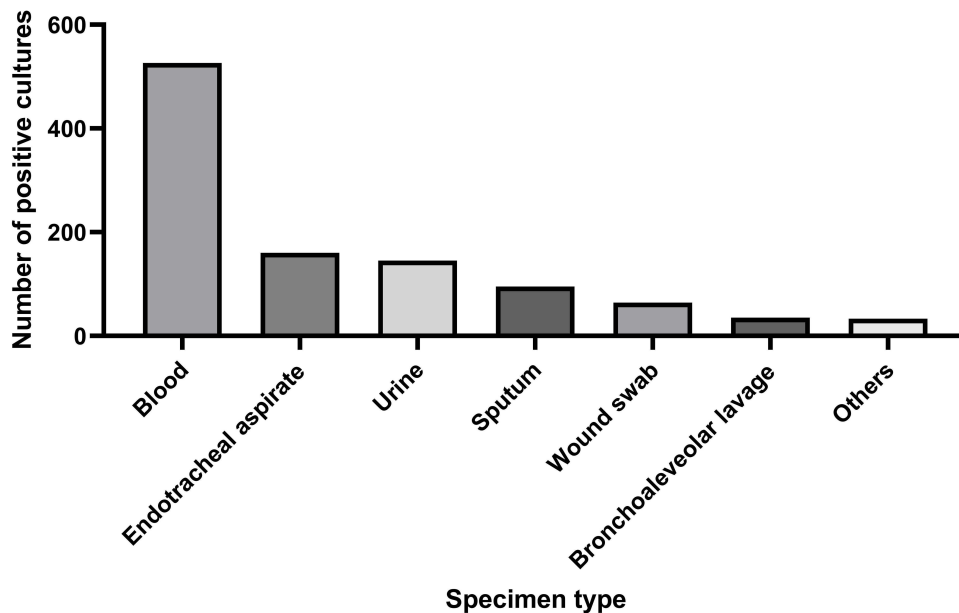

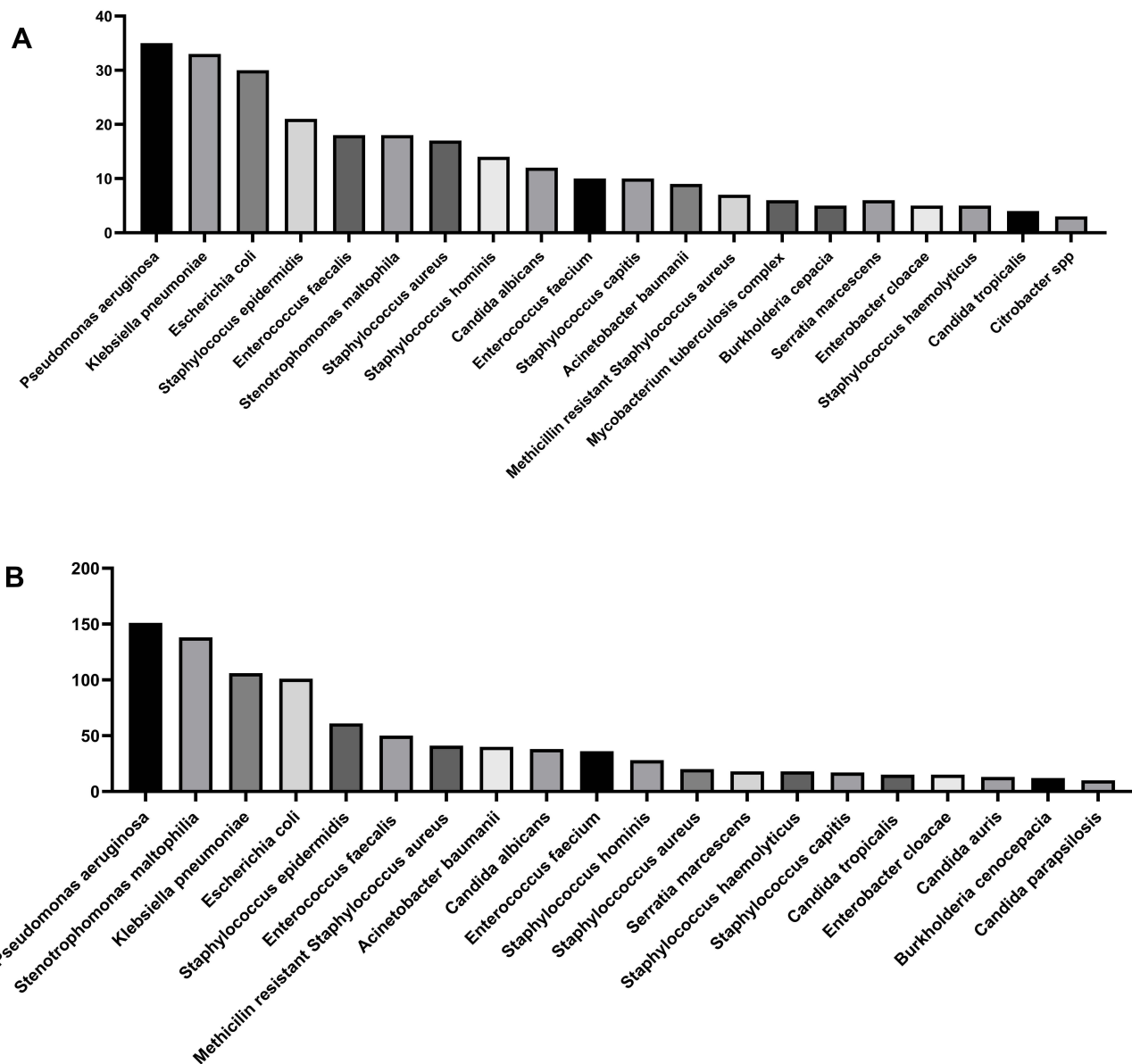**Figure 2** Distribution of specimen sources for positive cultures.

Figure 3 The top 20 microorganisms identified from first positive cultures and across duration of hospitalization. (**A**) Microorganisms identified from the first positive cultures obtained; (**B**) Microorganisms identified from all positive cultures obtained during hospitalization.

patients infected with SARS-CoV2 and the microbiological profile of the spectrum of causative agents remains a crucial knowledge gap in the literature. Specifically, we identified the absence of relevant epidemiological data from our region on the pattern of coinfections among COVID-19 patients, and this is the first study focusing on this coinfection pattern.

The findings from this study indicated that there is a low incidence of laboratory-confirmed coinfections among hospitalized COVID-19 patients in our setting. We also found that clinical outcomes worsened if

patients were in ICUs requiring high-level clinical care. In a report from Iran, a 12.4% occurrence of bacterial infections was reported among 340 patients with COVID-19.[14] In a large systematic review of 30 studies, bacterial coinfection was reported in 7% of patients hospitalised with COVID-19, which increased to 14% when only ICU patients were reported.[10] Similarly, a review of nine studies from China and the US showed that among 806 patients with COVID-19, 62 (8%) developed bacterial and fungal coinfections.[15] Among 338 patients hospitalized with COVID-19 in

Table 3 Distribution of antimicrobial susceptibility in positive cultures

Antibiotics	Positive cultures tested (n)	Sensitive (n)	%
Amikacin	73	44	60%
Amoxicillin/clavulanic acid	69	11	16%
Ampicillin	171	50	29%
Aztreonam	2	1	50%
Cefepime	130	65	50%
Cefotaxime	94	25	27%
Ceftazidime	110	38	35%
Ceftalozane tazobactam	3	3	100%
Ceftriaxone	8	5	63%
Cefuroxime	20	18	90%
Ciprofloxacin	225	73	32%
Clindamycin	49	4	8%
Ertapenem	74	49	66%
Erythromycin	118	4	3%
Fosfomycin	63	26	41%
Fusidic acid	93	16	17%
Gentamicin	134	91	68%
Gentamicin (high-level resistance)	9	4	44%
Imipenem	120	37	31%
Levofloxacin	44	43	98%
Linezolid	143	140	98%
Meropenem	114	86	75%
Metronidazole	2	2	100%
Moxifloxacin	31	1	3%
Nitrofurantoin	73	13	18%
Norfloxacin	52	38	73%
Oxacillin	130	16	12%
Penicillin G	150	1	1%
Piperacillin tazobactam	75	30	40%
Teicoplanin	185	169	91%
Tetracycline	78	17	22%
Tigecycline	82	81	99%
Trimethoprim	283	129	46%
Vancomycin	245	239	98%
Antifungals			
Amphotericin B	36	36	100%
Caspofungin	41	40	98%
Fluconazole	34	30	88%
Flucytosine	45	45	100%
Micafungin	44	44	100%
Voriconazole	33	32	97%

New York, a 6% rate of bacteremia was found,[16] whilst Zhou et al reported a 15% rate of bacterial coinfection, with 96% mortality.[17] However, these studies did not indicate if these were nosocomial infections nor did they provide information on how many of these patients required critical care. In contrast to these reports, our findings showed much lower rates of coinfections in patients hospitalized with COVID-19. Our finding of worsened clinical outcomes among those in ICUs requiring high-level clinical care is in keeping with the higher incidence of sepsis and mortality reported among COVID-19 patients in these units.[18–20]

Findings from the few patients with molecular screening suggested that viral coinfection and specifically Middle East respiratory syndrome coronavirus was not detected. This is similar to a report from Saudi Arabia.[21] Furthermore, based on the median interval between admission and first positive-culture report, we surmise that a majority of our patients had nosocomial infections, which is of significance, as initiation of empirical antimicrobial therapy using broad-spectrum antibiotics was commenced very early. This is in keeping with previously reported work that showed that bacterial coinfection was rarely documented in COVID-19 patients at admission and suggests that careful review of routine initiation of empirical antibiotics in COVID-19 patients is warranted.[22]

Our findings indicate that Gram-negative pathogens maintained an overall predominance as causative agents of initial and subsequent infections. This finding of a predominance of Gram-negative bacteria is in keeping with a pattern reported in a systematic review of 30 studies reporting coinfections in 3,834 patients with COVID-19.[22] Although there was variability in antimicrobial resistance, the bacterial isolates showed a higher trend of antibiotic resistance than the fungal isolates, which had high sensitivity to the antifungal tested. Additionally, commonly used empirical antibiotics were infrequently tested or exhibited low susceptibility profiles. Our findings also indicate that carriage of *mecA*, *ESBL*, *AmpC*, and carbapenemase-resistance genes were prevalent among the isolates identified. This is in keeping with the high occurrence of isolates harboring these resistance genes in our setting.[23–25] As such, it is important that this molecular epidemiological pattern be factored into the selection of empirical antibiotics.

The emergence of fungal agents, especially *C. auris* and *C. parapsilosis*, during subsequent cultures is of concern. Although other reports have identified COVID-associated pulmonary aspergillosis as a frequent coinfection in critically ill patients, our findings did not reflect this.[26] However, as higher occurrence of poor clinical progression and mortality has been reported for COVID-19 patients with fungal coinfections, this finding remains worrisome.[26–30] We hypothesize that the increment in fungal infections was most likely due to the acquisition of these pathogens in the hospital setting and the higher susceptibility of the patients, given their treatment with broad-spectrum antibiotics and immunosuppressive therapies.[27] This could also explain why some of our patients subsequently had multiple organisms cultured from different body sites during the clinical course of their illness.

A limitation of this study is that data of patients hospitalized with COVID-19 infection who did not develop coinfections was not obtained. We recommend that future work include such data to enable comparative analysis.

Conclusion

This is the first descriptive report on coinfections among patients hospitalized with COVID-19 in our setting. Although the occurrence of these coinfections was low, patients demonstrated a tendency toward poor clinical outcomes. Additionally, the predominance of Gram-negative pathogens, emergence of *Candida* infections, and presence of bacterial isolates harboring drug-resistant genes are of concern. We recommend that clinicians remain mindful of these factors in their selection of empirical antimicrobial agents. Furthermore, utilization of rapid bacteriological testing approaches coupled with antimicrobial-stewardship programs to ensure judicious use of antibiotics in the context of COVID-19 is crucial.

Disclosure

The authors report no conflicts of interest in this work.

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