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Clinical characteristics and risk factors for the isolation of multi-drug-resistant Gram-negative bacteria from critically ill patients with COVID-19

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SUMMARY

Background: We investigated the clinical characteristics and risk factors for the isolation of multi-drug-resistant (MDR) Gram-negative bacteria (GNB) from critically ill COVID-19 patients.

Methods: We retrospectively matched (1:2) critical COVID-19 patients with one or more MDR GNB from any clinical specimen (cases), with those with no MDR GNB isolates (controls).

Results: Seventy-eight cases were identified (4.5 per 1000 intensive care unit (ICU) days, 95% confidence interval (CI) 3.6–5.7). Of 98 MDR GNB isolates, the most frequent species were *Stenotrophomonas maltophilia* (24, 24.5%), and *Klebsiella pneumoniae* (23, 23.5%). Two (8.7%) *K. pneumoniae*, and six (85.7%) *Pseudomonas aeruginosa* isolates were carbapenem resistant. A total of 24 (24.5%) isolates were not considered to be associated with active infection. Those with active infection received appropriate antimicrobial agents within a median of one day. The case group had significantly longer median central venous line days, mechanical ventilation days, and hospital length of stay ($P < 0.001$ for each). All-cause mortality at 28 days was not significantly different between the two groups ($P = 0.19$). Mechanical ventilation days (adjusted odds ratio 1.062, 95% CI 1.012–1.114; $P = 0.015$), but not receipt of corticosteroids or tocilizumab, was independently associated with the isolation of MDR GNB. There was no association between MDR GNB and 28-day all-cause mortality (adjusted odds ratio 2.426, 95% CI 0.833–7.069; $P = 0.104$).

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Conclusion: In critically ill COVID-19 patients, prevention of MDR GNB colonization and infections requires minimizing the use of invasive devices, and to remove them as soon as their presence is no longer necessary.

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Introduction

By 23rd January 2021, the global reported cases of SARS-CoV-2, the cause of COVID-19, had exceeded 96 million with more than two million associated deaths [1]. Up to 10% of patients with COVID-19 may develop critical disease and require admission to an intensive care unit (ICU) [2]. COVID-19 is associated with higher overall mortality in older patients, and in those with chronic medical conditions [2].

The overall incidence of bacterial infection in hospitalized COVID-19 patients has been estimated at 15.5% [3]. However, most existing reports described bacterial and viral co-infections, defined as those present at the time of COVID-19 diagnosis. The majority of these were caused by respiratory viruses or community-acquired bacterial pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [3,4]. Conversely, bacterial secondary infections are defined as those emerging during the course of illness or hospital stay [3]. Relatively few data are available on secondary bacterial infections with COVID-19, especially those caused by multi-drug-resistant (MDR) Gram-negative bacteria (GNB) in critically ill COVID-19 patients [5].

Critically ill patients in general are at increased risk of MDR Gram-negative infections [6]. It is not clear, however, if specific risk factors determine which critical COVID-19 patients develop secondary MDR GNB infections. The aim of this study was to describe the clinical and microbiological characteristics, and to explore their risk factors for the isolation of MDR GNB from critically ill COVID-19 patients. A better understanding of these aspects could inform prevention strategies, early recognition and appropriate treatment, and ultimately improve clinical outcomes.

Materials and methods

Materials and setting

Hamad Medical Corporation (HMC) provides medical care for all COVID-19 patients in Qatar. Three intensive care units, with a total capacity of 277 beds, were dedicated to COVID-19 patients. To meet the increased clinical care load, medical and nursing staff were redeployed from non-critical care areas. Introductory ICU infection prevention training was provided for the redeployed personnel.

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board (IRB) at Hamad Medical Corporation approved this study (MRC-05-158). The IRB determined that the study was exempt under category 3 and waived the need for informed patient consent.

SARS-CoV-2 infection was diagnosed by real-time polymerase chain reaction (RT-PCR) assays on respiratory tract

specimens. Severity of COVID-19 was classified according to the World Health Organization (WHO) guidelines [7].

Standard care for patients with critical COVID-19 involved appropriate supportive care, in addition to investigational antivirals (e.g., hydroxychloroquine, azithromycin, lopinavir/ritonavir, and interferon alpha 2a), and immunomodulating therapy (e.g., corticosteroids, and tocilizumab). Individual regimens were selected by the treating physicians based on the presence of contra-indications or potential drug–drug interactions, and the patients' preferences. Local infection control guidelines for care of patients with COVID-19 in ICU included wearing disposable gloves, long-sleeved gowns, and face shields during all types of direct patient contact. N95 face masks were used during aerosol-generating procedures; otherwise, a surgical mask was acceptable. The guidelines stipulated that all personal protective equipment should be changed before moving from one patient to another. Alcohol-based hand gels were to be used before and after donning and doffing of personal protective equipment. All environmental surfaces in clinical areas were cleaned by trained housekeeping personnel using 0.1% chlorine-based detergents (Actichlor, Ecolab, Saint Paul, MN, USA). Cleaning was performed twice per day, and at patient transfer or discharge [8].

Bacterial identification and susceptibility testing

Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Corporation, Billerica, MA, USA) was used for bacterial identification. BD Phoenix™ (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) was used for antimicrobial susceptibility testing and for the detection of extended-spectrum beta-lactamases (ESBLs). Clinical Laboratory Standards Institute breakpoints were used [9]. When an MDR Gram-negative species was isolated from multiple sites or on multiple occasions from the same patient, only the first isolate was included.

Procedures

GNB isolates were considered MDR if they expressed in-vitro resistance to one or more antimicrobial agents from three or more antimicrobial classes [10]. The National Healthcare Safety Network definitions were used to define and classify bacterial infections [11].

The electronic health records were used to identify patients who were aged 18 years or more, had laboratory-confirmed COVID-19, and were admitted to ICU for 48 h or more during the period from 1st March 2020 to 30th June 2020. Cases were defined as those who had at least one MDR GNB species isolated from any biological specimen taken during their ICU admission. Controls were defined as those who did not have any MDR Gram-negative isolates during their ICU stay. Cases and controls were matched in 1:2 ratio for their month of admission to ICU. Starting from 1st March

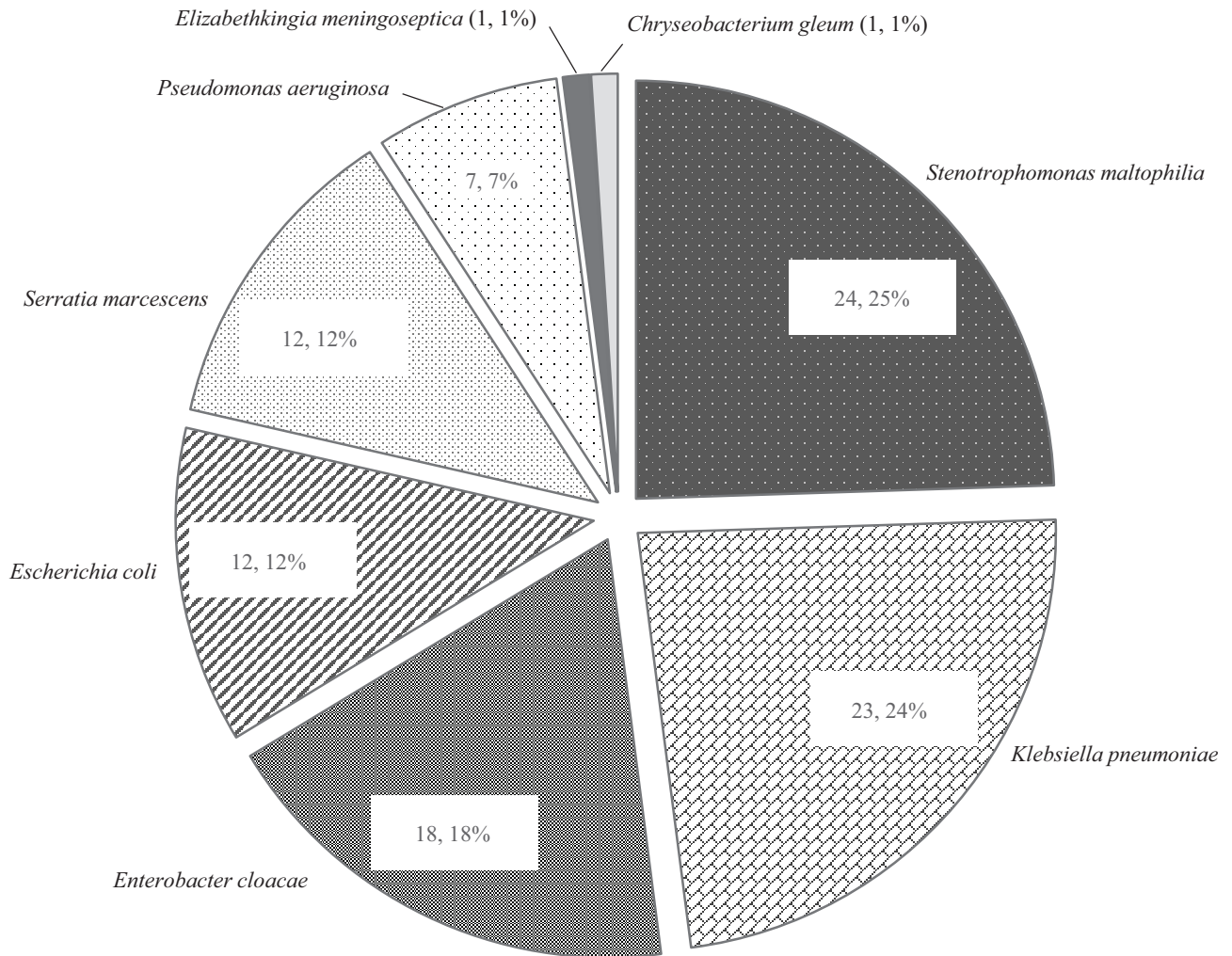


Figure 1. Species breakdown for multi-drug resistant Gram-negative bacteria isolated from critically ill COVID-19 patients. Data presented as number (percentage).

2020, consecutive patients who were eligible for inclusion were selected until two controls were identified for each case. Study data were collected retrospectively during the period from 15th July 2020 to 14th August 2020. The report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [12].

Statistical analysis

Data were summarized as numbers (percentages) or medians and interquartile ranges (IQR), and were compared using Fisher's exact test or Wilcoxon rank-sum test, as appropriate. Wald method was used to estimate the 95% confidence interval (CI) around the estimated incidence of MDR GNB isolation. A logistic regression model with stepwise backward selection was used to identify covariables associated with the MDR GNB isolation. Covariables with $P < 0.1$ in the univariate analysis were included in a multi-variate logistic regression analysis. Statistical analyses were performed using Stata Statistical Software, Release 15 (StataCorp., College Station, TX, USA).

Results

A total of 78 cases were identified out of 1231 adults who were admitted to ICU with COVID-19 during the study period (incidence 4.5 per 1000 ICU days, 95% CI 3.6–5.7). Overall, the study included 234 individuals, 212 (90.6%) were males, and the median age was 40 years (IQR, 40–60). Most patients were nationals of countries in the WHO's South East Asia region (144, 61.5%), or East Mediterranean region (63, 26.9%). Diabetes mellitus (88, 37.6%), and hypertension (84, 35.9%) were the most frequent co-existing medical conditions.

Within 90 days prior to the COVID-19-related hospital admission, 11 (4.7%) patients had been hospitalized, two (0.85%) had had MDR GNB infection or colonization, and six or fewer individuals had received cephalosporin, quinolone, or carbapenem therapy.

A total of 98 MDR GNB isolates were retrieved from patients in the case group within a median of 9 days (IQR, 4–14) of admission to ICU. More than one MDR GNB were isolated from 17 (21.8%) patients. The most frequent sample sites were the respiratory tract (74, 75.5%), blood (18, 18.4%), and urine (6, 6.1%). The most frequently isolated MDR Gram-negative

Table 1
Clinical characteristics by group

Variable	Total (N = 234)	Control (N = 156)	Case (N = 78)	P
Male sex	212 (90.6%)	138 (88.5%)	74 (94.9%)	0.15
Age	49 (40–60)	46.5 (38–58.5)	52 (42–61)	0.085
Nationality by WHO region of origin				
South-East Asia Region	144 (61.5%)	98 (62.8%)	46 (59%)	
Eastern Mediterranean Region	63 (26.9%)	42 (26.9%)	21 (26.9%)	
Western Pacific Region	21 (9%)	12 (7.7%)	9 (11.5%)	
African Region	5 (2.1%)	3 (1.9%)	2 (2.6%)	
Region of the Americas	1 (0.4%)	1 (0.6%)	0	
Co-existing medical condition				
Diabetes mellitus	88 (37.6%)	61 (39.1%)	27 (34.6%)	0.50
Hypertension	84 (35.9%)	58 (37.2%)	26 (33.3%)	0.56
Chronic heart disease	28 (12%)	20 (12.8%)	8 (10.3%)	0.57
Chronic lung disease	18 (7.7%)	11 (7.1%)	7 (9%)	0.60
Connective tissue disease	4 (1.7%)	3 (1.9%)	1 (1.3%)	1.00
Active malignancy	6 (2.6%)	6 (3.9%)	0	0.18
Organ transplantation	2 (0.9%)	0	2 (2.6%)	0.11
Within the preceding 90 days				
Hospitalization	11 (4.7%)	10 (6.4%)	1 (1.3%)	0.11
ICU admission	3 (1.3%)	3 (1.9%)	0	0.55
Surgical procedures	2 (0.9%)	2 (1.3%)	0	0.55
MDR infection or colonization	2 (0.9%)	1 (0.6%)	1 (1.3%)	1.00
Cephalosporins	6 (2.6%)	4 (2.6%)	2 (2.6%)	1.00
Meropenem	2 (0.9%)	1 (0.6%)	1 (1.3%)	1.00
Quinolones	2 (0.9%)	2 (1.3%)	0	0.55
Corticosteroids	11 (4.7%)	6 (3.9%)	5 (6.4%)	0.38
Current or past smoker	12 (5.1%)	6 (3.9%)	6 (7.7%)	0.32
Days from symptoms onset to hospitalization	5 (3–7)	5 (3–7)	5 (3–6)	0.43
Baseline blood investigations				
Peripheral white cell count ($\times 10^9/L$)	9.3 (6.3–12.2)	9.2 (6.4–11.6)	10.1 (5.9–13.7)	0.44
Peripheral absolute neutrophil count ($\times 10^9/L$)	7.8 (4.9–10.8)	7.6 (4.9–10.2)	8.4 (4.8–11.6)	0.31
Peripheral absolute lymphocyte count ($\times 10^9/L$)	0.8 (0.6–1.3)	0.9 (0.6–1.3)	0.8 (0.6–1)	0.30
C-reactive protein mg/L	164.8 (96–239)	155 (94–238)	182 (107–255)	0.45
Procalcitonin (pg/L)	0.5 (0.2–1.3)	0.4 (0.2–1.1)	0.7 (0.2–1.7)	0.20
Serum creatinine ($\mu\text{mol/L}$)	81.5 (70–104)	78 (68.5–100.5)	87 (74–117)	0.014
Serum albumin (g/L)	28 (24–31)	28 (24–31)	28 (24–30)	0.54
Ferritin ($\mu\text{g/L}$)	980 (640–1557)	900 (609–1390)	1070 (750–1933)	0.008
D-dimer (mg/L)	980 (640–1557)	1.1 (0.6–2.5)	1.8 (0.6–5.2)	0.026
Supportive care and investigational therapies				
SOFA Score	5 (3–8)	4 (2–7)	6 (4–8)	0.002
Urinary catheterization	169 (72.2%)	99 (63.5%)	70 (89.7%)	<0.001
Mechanical ventilation days	4 (0–11)	3 (0–6)	12.5 (5–25)	<0.001
Central line days	7 (0–16)	5 (0–9)	15 (7–28)	<0.001
Renal replacement therapy	35 (15%)	19 (12.2%)	16 (20.5%)	0.092
Hydroxychloroquine	228 (97.4%)	153 (98.1%)	75 (96.2%)	0.40
Azithromycin	226 (96.6%)	150 (96.2%)	76 (97.4%)	0.72
Lopinavir-ritonavir	136 (58.1%)	87 (55.8%)	49 (62.8%)	0.30
Interferon alpha 2-a	13 (5.6%)	8 (5.1%)	5 (6.4%)	0.69
Total tocilizumab doses	1 (0–1)	1 (0–1)	1 (1–2)	0.004
Total methylprednisolone doses	6 (5–8)	5 (5–7)	6 (5–10)	0.001
Clinical outcomes				
Hospital length of stay (days)	23 (16–34)	20 (15–30)	31.5 (20–48)	<0.001
ICU duration days (days)	11 (7–20)	9 (6–14)	20 (11–31.9)	<0.001
Hospital discharge by day 28	142 (60.7%)	115 (73.7%)	27 (34.6%)	<0.001
ICU discharge by day 28	198 (84.6%)	145 (92.9%)	53 (67.9%)	<0.001
All-cause mortality by day 28	27 (11.5%)	15 (9.6%)	12 (15.4%)	0.19

Data are presented as number (percentage) or median (interquartile range). ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; WHO, World Health Organization.

*Antimicrobial therapy duration up to the date of isolation of the first multi-drug resistant Gram-negative bacteria from any clinical specimen.

species were *Stenotrophomonas maltophilia* (24, 24.5%), *Klebsiella pneumoniae* (23, 23.5%), and *Enterobacter cloacae* (18, 18.4%) (Figure 1). ESBL production was demonstrated in the majority of *K. pneumoniae* (19, 82.6%), *E. cloacae* (13, 72.2%), *E. coli* (11, 91.7%), and *S. marcescens* (10, 83.3%) isolates. Two (8.7%) *K. pneumoniae*, and six (85.7%) *P. aeruginosa* isolates were carbapenem resistant. A total of 24 (24.5%) isolates, 21 from the respiratory tract and three from urine samples, were not considered to be associated with active infection. Those with active infection received at least one microbiologically active antimicrobial agent within a median of one day (IQR 0–3) from date of isolation of MDR GNB from their clinical sample.

The case group differed significantly from the control group in their median Sequential Organ Failure Assessment (SOFA) scores (6 vs 4, $P=0.002$), central venous line days (15 vs 5 days, $P<0.001$), mechanical ventilation days (12.5 vs 3 days, $P<0.001$), and the proportion with indwelling urinary catheters (89.7 vs 63.5%, $P<0.001$) (Table I). Moreover, the median number of doses of tocilizumab ($P=0.004$) and methylprednisolone ($P=0.001$) was significantly higher in the case group, as were median baseline serum creatinine (87 vs 78 $\mu\text{mol/L}$, $P=0.014$), serum ferritin (1070.5 vs 900 $\mu\text{g/L}$, $P=0.008$), and D-dimer (1.8 vs 1.1 mg/L , $P=0.026$). Other baseline and clinical characteristics are summarized in Table I.

The median hospital length of stay was 31.5 days (IQR 20–48) for the case group, and 20 days (IQR 15–30) for the control group ($P<0.001$). However, 12 (15.4%) from the case group and 15 (9.6%) from the control group died of any cause within 28 days of admission to ICU ($P=0.19$). Other clinical outcomes are shown in Table I.

In the unadjusted logistic regression analysis, several covariates showed statistically significant associations with the isolation of MDR GNB; but mechanical ventilation days was the only variable with a significant independent association

(adjusted odds ratio 1.062, 95% CI 1.012–1.114; $P=0.015$) (Table II). The isolation of MDR GNB was not associated with 28-day all-cause mortality (adjusted odds ratio 2.426, 95% CI 0.833–7.069; $P=0.104$) (Supplementary Tables S1 and S2).

Discussion

We herein report the rate and risk factors for the isolation of MDR GNB from a national cohort of critically ill COVID-19 patients. The most frequently identified MDR pathogen was *S. maltophilia*, an established cause of nosocomial sporadic infections and outbreaks [13]. *S. maltophilia* are typically susceptible to a limited number of antimicrobial agents and their treatment is often challenging [13]. The other frequently isolated MDR GNB in our report included *K. pneumoniae*, *E. cloacae*, *E. coli* and *P. aeruginosa*, all of which are typical nosocomial pathogens [6]. It is possible that some of these were part of one or more point outbreaks. Unfortunately, the study isolates were not available for epidemiological typing to allow the investigation of this possibility.

Severe COVID-19 has been associated with excessive antimicrobial prescribing, often in the absence of documented bacterial infection [14]. Prior exposure to broad-spectrum antimicrobials is an established risk factor for MDR Gram-negative colonization and infection [6]. This was notably uncommon in our study. One possible explanation for this is that our study population was younger and with fewer chronic medical conditions compared with critical COVID-19 cohorts reported from other parts of the world [15].

Conversely, prolonged use of external devices such as urinary catheters, central venous lines and mechanical ventilation, was significantly more prevalent in those from whom MDR GNB were isolated compared with the control group. Indeed, mechanical ventilation days was the single

Table II

Logistic regression for the isolation of multi-drug resistant Gram-negative bacteria from critically ill COVID-19 patients

Variable	Univariate logistic regression			Multi-variate logistic regression		
	Unadjusted odds ratio	95% Confidence interval	<i>P</i>	Adjusted odds ratio	95% Confidence interval	<i>P</i>
Age	1.014	0.994–1.035	0.161	–	–	–
Male sex	2.413	0.787–7.392	0.123	–	–	–
Hospitalization within the preceding 90 days	0.189	0.023–1.508	0.116	–	–	–
Diabetes mellitus	0.824	0.468–1.453	0.504	–	–	–
Hypertension	0.845	0.477–1.497	0.563	–	–	–
Chronic heart disease	0.778	0.326–1.854	0.570	–	–	–
Chronic lung disease	1.299	0.483–3.495	0.604	–	–	–
SOFA score	1.142	1.046–1.246	0.003	1.066	0.954–1.187	0.265
Mechanical ventilation days	1.085	1.053–1.119	<0.001	1.062	1.012–1.114	0.015
Central line days	1.064	1.039–1.089	<0.001	1.010	0.973–1.049	0.599
Renal replacement therapy	1.860	0.897–3.859	0.095	0.560	0.219–1.431	0.226
Urinary catheterization	5.037	2.261–11.22	<0.001	1.661	0.639–4.318	0.298
Tocilizumab doses	1.666	1.182–2.349	0.004	0.995	0.647–1.530	0.981
Methylprednisolone doses	1.139	1.059–1.224	<0.001	1.044	0.952–1.146	0.358
Ferritin	1.000	0.999–1.000	0.680	–	–	–
D-dimer	1.013	0.992–1.034	0.229	–	–	–
Serum creatinine	1.001	0.999–1.003	0.236	–	–	–

GNB, Gram-negative bacteria; MDR, multi-drug resistant; SOFA, Sequential Organ Failure Assessment.

independent risk factor for the isolation of MDR GNB from our critically ill COVID-19 cohort. Guidelines for infection prevention in ICU promote limiting the use of external devices, and emphasize the need for their proper handling [6]. In our setting, as in many others [15,16], the unprecedented influx of large numbers of critically ill COVID-19 patients requiring ICU support necessitated the deployment of medical and nursing staff who were less familiar with the ICU environment. Despite the provision of orientation and basic infection prevention training, such relative inexperience may have contributed to the observed secondary MDR GNB infections [17].

The acquisition of MDR GNB in a heightened infection prevention and control setting such as that associated with COVID-19 might seem counterintuitive. However, randomized control trials have failed to demonstrate significant reduction in ICU-acquired MDR bacterial infections with universal contact precautions [18,19]. Furthermore, it has been shown that compliance with contact isolation precautions deteriorates as the proportion of patients requiring such precautions increases [20]. To complicate matters even further, excessive wearing of gloves in ICU is associated with poor compliance with hand hygiene [21]. Other factors that can be detrimental to the effectiveness of infection control precautions include excessive workloads and staff burnout [22], both of which were not uncommon during peaks of the SARS-CoV-2 pandemic [15,23]. Understanding the above elements is important when planning and implementing the appropriate education, support and resource provision strategies to minimize the acquisition of MDR GNB in critically ill COVID-19 patients.

Earlier in the SARS-CoV-2 pandemic, observational studies suggested an association between the use of tocilizumab for severe COVID-19 and an increased risk of secondary infections [24]. In this report, such an association was not apparent. Results from a recent meta-analysis of tocilizumab in COVID-19 patients, which included higher quality observational studies and randomized clinical trials, are consistent with our finding [25]. Similarly, we found no independent association between receipt of systemic corticosteroids and the isolation of MDR GNB. This finding is reassuring, given the demonstrated mortality reduction with dexamethasone in patients with severe COVID-19 [26].

Infections caused by MDR pathogens are associated with increased mortality, length of hospital stay, and hospital costs [6]. This is at least in part due to delayed initiation of appropriate antimicrobial therapy [27]. Some early COVID-19 reports suggested that secondary bacterial infections were more likely in fatal COVID-19 than in survivors [28]. In this study, patients with MDR GNB required significantly longer periods of stay in ICU and in hospital, and were less likely to be discharged from the hospital within 28 days. However, the isolation of MDR GNB was not associated with increased mortality. This could at least in part be explained by two factors: the relatively young age and low comorbidity of the cohort, and the minimal delay in initiation of microbiologically active antimicrobial therapy for those with active infection.

In conclusion, our report identified prolonged mechanical ventilation is an important risk factor for the isolation of MDR GNB from critically ill COVID-19 patients. Strategies for the prevention of MDR GNB colonization and infection in COVID-19 patients should include efforts to minimize the use of invasive devices, and to remove them as soon as their presence is no longer necessary. Systemic corticosteroids and

tocilizumab were not associated with increased risk of MDR GNB isolation in critically ill COVID-19 patients.

Author contributions

Conceptualization, A.B., D.B., A.Z. and A.S.O.; methodology, A.B., A.A.E. and A.S.O.; data curation, A.B., A.A.E., D.B., A.Z., K.M.A., A.A.B., M.M.B.A., A.M.E. and G.A.M.A.; formal analysis, J.D. and A.S.O.; supervision, A.S.O.; resources, M.A.A., A.S.I and A.A.; writing – original draft, A.S.O. and A.B. All authors read and approved the final manuscript.

Conflict of interest statement

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Appendix A. Supplementary data

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