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Research Article

Outcome and Risk Factors for Acquisition of Multi-Drug Resistant Organisms among COVID-19 Patients, A Single Center Case Control Study

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Abstract

Introduction: Several recent reports have described an increase in multidrug-resistant organisms (MDROs) during the COVID-19 pandemic, and multiple factors identified.

Objectives: The primary objectives of the study are to determine the incidence of MDROs among hospitalized COVID-19 patients, the risk factors leading to infection or colonization with MDROs among these patients and the determinants of mortality among infected patients. The secondary objective is to study risk factors for mortality among the study cohort.

Method: A retrospective case-control study included all patients screened for MDROs on admission or detected later to have a positive sample for MDROs during their hospital stay (April-September 2020). Associations were tested using chi-square and independent t-tests. For the adjusted analysis, Multivariate logistic regression applied. P<0.05 was considered as statistical significance.

Result: The total number of patients included was 313. 33.2% (n=104) were MDRO-infected or colonized patients, and 66.8% (n=209) were controls. The incidence density during the study period of MDROs was 16.7 per 1000 patient days, and the incidence was 17. 9 per 100 admissions. The monthly incidence density of MDROs ranged from 7.0 per 1000 patient days to 30.6 per 1000 patient days and steadily increased. In univariate analysis, the length of ICU stays P <0.001, length of hospital stay P <0.001, receiving ventilation P0.001, having urinary catheter P0.004, tracheostomy P<0.001, NGT in situ P 0.001, receiving more than four antibiotics P<0.001 and having comorbidities P 0.001 were risk factors for acquiring MDROs. Comorbidities were independent factors for MDRO acquisition (OR 3.61, CI 1.37-9.61, P0.010). Mortality was higher among those with MDRO infection (50%, n=30) than those with colonization (31.8%, n=14). Only receiving a few antibiotics was related to worse outcomes (OR 3.09, CI; 1.13-8.44, P0.028). The independent risk factors for mortality among the study cohort were age (OR 1.087 CI 1.06 to 1.1, P <0.001), and acute dialysis (OR 4.392, CI 1.82-10.61, P 0.001).

Conclusion: The acquisition of MDROs was not associated with worse outcomes among COVID-19 patients, although mortality was significantly higher among infected patients than colonized patients. Implementing strict infection prevention and control strategies is vital to prevent colonization and progression to infection among colonized patients.

Keywords: COVID-19; MDRO; Risk factors; Mortality

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Introduction

Several recent reports have described an increase in multi-drug-resistant organisms (MDROs) during the COVID-19 pandemic [1]. Dona` D et al. and others highlighted factors leading to the surge of MDROs among COVID-19 patients, such as high use of broad-spectrum antibiotics in the hospital setting, high rates of admission, shortages of staff and personal protective equipment (PPE), and high-acuity patients with prolonged stays in overcrowded facilities. Moreover, severe COVID-19, which particularly affects elderly patients with multiple comorbidities, may be important in determining changes in colonization pressure [2].

A recent study conducted in intensive care units (ICUs) in 88 countries showed that although only 54% (8135/15 165) of patients had suspected or proven bacterial infection, 70% (10 640/15 165) of them had received at least one antibiotic either for prophylaxis or treatment purposes [3].

M. Polly et al. found that the overall identification of MDROs increased by 23%(P<.005) during COVID-19, and the overall pathogen analysis shows significant increases in infection by CRAB (carbapenem-resistant *Acinetobacter baumannii*) and MRSA (Methicillin-resistant *Staphylococcus aureus*) (+108.1%,p<0.005:+94.7%p&lt0.005) respectively, but not CRE (Carbapenem-resistant Enterobacteriaceae), CRP (Carbapenem-resistant *Pseudomonas aeruginosa*) or VRE (Vancomycin-resistant Enterococcus) which might indicate outbreaks during the pandemic [4].

Karruli et al. reported that fifty per cent of patients developed an MDR infection during ICU stay after a median time of 8, MDR infections were linked to a higher length of ICU stay (p = 0.002), steroid therapy (p = 0.011), and associated with a lower ICU mortality (odds ratio: 0.439,95% confidence interval: 0.251–0.763; p < 0.001) [5].

The primary objectives of the study are to determine the incidence of MDROs among hospitalized COVID-19 patients, the risk factors leading to infection and/or colonization with MDROs among these patients and the determinants of mortality among infected patients. The secondary objective is to study risk factors for mortality among the study cohort.

Method

Background

The study was conducted in a tertiary care hospital, a retrospective case-control study among COVID-19 patients admitted in the first six months of the pandemic (April-September 2020). The hospital has 800 beds and an adult general medical/surgical ICU with a bed capacity of 12 beds with a step-down care unit of 12 beds. During the COVID-19 crisis, the general ICU for non-COVID-19 patients contracted to 8 beds capacity caring for critical non-COVID-19 patients. Another surgical ICU was converted to a COVID-19 critical unit, where the capacity reached 50 beds at the peak of the pandemic. In addition, stable confirmed COVID-19 patients were admitted to general ambulatory isolation wards that were opened for this purpose according to the need. Active MDROs surveillance cultures were collected for all admitted COVID-19 patients, which included MRSA, CRE, MDRA [Multi-Drug Resistant Acinetobacter baumannii] and Candida auris. The MDRO surveillance was initially applied to critical COVID-19 patients only and expanded in May 2020 to include stable COVID-19 patients.

Population

The study included all positive COVID-19 patients admitted to Royal Hospital (RH) in COVID-19 ambulatory wards (non-critical patients) and Critical COVID-19 wards between April to September 2020 and had a positive screening sample or clinical sample for MDROs during their COVID-19 care admission. COVID-19 patients who were not screened or did not grow any MDRO from clinical samples were excluded. Controls were chosen from COVID-19 patients who had negative active surveillance culture with a patient-control ratio of 1:2. No matching was applied.

Definitions

A case was defined as a positive COVID-19 patient who tested positive for one or more of the MDRO from either screening or a clinical sample or both during their hospital stay in the study period.

A control was defined as a COVID-19 patient admitted to the hospital during the study period and tested negative for the MDRO screening test and did not have a positive clinical sample for MDRO throughout their hospital stay.

Hospital-acquired was defined as a positive screening culture for MDRO or clinical samples after 48 hours of admission to our hospital.

Other hospital acquisition was defined as a positive culture for MDRO detected in less than 48 hours of hospital transfer or having a history of admission within that hospital in the last three months.

Community-acquired was defined as a positive culture for MDRO from a screening or clinical sample and no recent admissions to healthcare institutions within the last three months.

Multi-Drug Resistant Organisms are bacteria and other microorganisms that have developed resistance to antimicrobial drugs. Common examples of these organisms include: MRSA VRE, CRE, MDRA, MDRP ana *C. auris*.

Microbiological Method

Active surveillance cultures for MDROs were collected according to the criteria in the hospital policy attached in appendix 1. Screening samples were inoculated into Chromogenic agar. The antimicrobial susceptibility testing in the laboratory is interpreted according to the Clinical & Laboratory Standards Institute (CLSI) with standardized susceptibility testing methods. Multidrug-resistant organisms are alerted by the laboratory using an electronic alert system according to the MDRO definitions for each organism described in ppendix1. The list is then communicated to the infection prevention and control team daily.

The incidence of MDROs was calculated as the number of new MDROs detected divided by the total admission for that month multiplied by 100 admissions, and the incidence density of MDROs was calculated as the number of new MDROs detected divided by patient days for that month multiplied by 1000. The MDRO detected for each patient is counted once only.

Data collection

Demographic data, risk factors and length of hospital stay where collected from the hospital electronic system (AL Shifa+).

Statistical analysis

All the collected information was analyzed using IBM SPSS Statistics 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). For descriptive purposes, categorical information was presented using frequency and percentages, and continuous information was presented using mean with standard deviation. Categorical associations were made using the chi-square test, and continuous information with categorical was tested using the independent 't-test. Significant factors and p<0.2 were taken into multivariate logistic regression for the adjusted analysis. A P-value of <0.05 was considered statistically significant.

Research ethics

The study was approved by the Hospital scientific. research ethics (SRC#91/2020).

Results

The total number of patients included was 313, 104 (33.2%) were MDRO-infected or colonized cases, and 209 (66.8%) were controls. The mean age was 55.7±16.03, 69.6% (n= 218) were males, and 30.4% (n=95) were females. One thousand one hundred thirty-nine screening samples were processed during the study period. Only 38 tests came positive (positivity rate = 3.3%).

Significant risk factors for acquiring MDROs among COVID-19 patients in univariate analysis were the length of ICU stay P<0.001, length of hospital stay P<0.001, receiving ventilation P0.001, having urinary catheters P0.004, having tracheostomy P<0.001, NGT in situ P0.001, receiving more than four antibiotics P<0.001 and having co-morbidities P <0.001. However, in multivariate analysis, only co-morbidities were significant OR3.61, CI1.37-9.61, P0.010 **(Table 1)**.

The overall incidence density of MDROs was 16.7 per 1000 patient days, and the overall incidence was 17. 9 per 100 admissions. The monthly incidence density of MDROs ranged from 7.0 per 1000 patient days to 30.6 per 1000 patient days, steadily increasing as the number of admissions increased **(Table 2**).

The total MDRO detected among cases was 135. 34.1% (n=46) of these were ESBLs (Extended Spectrum Beta-Lactamases), Followed by CRE 24.4% (n=33), MRSA 15.6% (n=21), MDRA 12.6% (n=17). MDRPs accounted for 4.4% (n=6), while VRE and C. auris accounted for 5.2% (n=7) and 3.7% (n=5), respectively. Details of MDROs incidence are given in Table 2. 47 (34.8%) of MDROs caused colonization; however, 88 (65.2%) caused infections. The majority of acquisitions, 68.9% (n=93), were attributed to our hospital, 24.4% (n=33) were acquired in other hospitals, while 6.7% (n=9) were community-associated, mostly ESBLs and MRSA. 70.2% (n=73) of MDRO-positive patients had one MDRO during their hospital stay, while 22.0% (n=23) patients acquired 2 MDROs and 3.8% (n=4) patients acquired 3 MDROs **Table 2**.

In the sub-analysis of MDRO infected/colonized cases, mortality among those infected was 50% (n=30), compared to those colonized only 31.8% (n=14), P 0.073. The determinants of mortality among MDROs positive COVID-19 patients were having a tracheostomy P 0.024, receiving < 4 antibiotics P0.002, Length of hospital stay P <0.001 and length of ICU stay P 0.009. However, in multivariate analysis, only receiving less than four antibiotics was significant OR 3.09, CI; 1.13 – 8.44, P 0.028, as shown in **Table 3**.

Risk Factors for mortality among the study cohort in univariate analysis were age P<0.001, length of ICU stay P0.045, invasive devices, pronning P0.027 and acute dialysis <0.001. In multivariate analysis, only age OR 1.087 CI 1.06 to 1.1, P <0.001 and acute dialysis OR 4.392, CI 1.82-10.61, P 0.001were statistically significant as shown in **Table 4**.

Table 1: Clinical characteristics by group and logistic regression for the MDROs Acquisition.

Variables	Total (n=313)	Controls (n=209)	Cases (n=104)	p-Value	Multi-variate logistic regression		
	n (%)	n (%)	n (%)		Adjusted odds ratio	95% C.I.	p-Value
Age	55.70±16.03	57.21±15.03	54.94±16.48	0.239			
Male	218 (69.6)	149 (71.3)	69 (66.3)	0.434			
ICU admission	280 (89.5)	185 (88.5)	95 (91.3)	0.559			
Length of ICU stay	11 (5, 19)	8 (5, 13)	19 (10.8, 27.3)	<0.001			
Length of Hospital stay	14 (8, 24)	12 (7, 17)	29.49 (12, 43)	<0.001			
Ventilation	225 (71.9)	138 (66.0)	87 (83.7)	0.001	1.091	0.05-23.81	0.956
Urinary catheter	230 (73.5)	143 (68.4)	87 (83.7)	0.004	0.303	0.05-2.02	0.217
Tracheostomy	58 (18.5)	18 (8.6)	40 (38.5)	<0.001			
NGT	225 (71.9)	138 (66.0)	87 (83.7)	0.001			
Number of pronning							
1	37 (24.5)	26 (30.2)	11 (16.9)	0.039			
2	45 (29.8)	28 (32.6)	17 (26.2)		1.164	0.39-3.47	0.785
3	39 (25.8)	21 (24.4)	18 (27.7)		0.741	0.22-2.53	0.632
4	19 (12.6)	9 (10.5)	10 (15.4)		1.225	0.31-4.86	0.773

5	8 (5.3)	1 (1.2)	7 (10.8)		8.263	0.80-85.76	0.077
6	3 (2.0)	1 (1.2)	2 (3.1)		7.882	0.50-124.09	0.142
Acute dialysis	46 (14.7)	27 (12.9)	19 (18.4)	0.234			
≥4 antibiotics	62 (19.8)	22 (10.50	40 (38.5)	<0.001	1.741	0.63-4.81	0.285
Comorbidities:	227 (72.5)	142 (67.9)	85 (81.7)	0.011	3.621	1.37-9.61	0.01
Cardiac	18 (5.8)	8 (3.8)	10 (9.6)	0.068			
Obesity	31 (9.9)	19 (9.1)	12 (11.5)	0.548			
Kidney	42 (13.4)	18 (8.6)	24 (23.1)	<0.001			
Diabetes Mellitus	161 (51.4)	94 (45.0)	67 (64.4)	0.001			
Lung	15 (4.8)	8 (3.8)	7 (6.7)	0.271			
Hypertension	155 (49.5)	100 (47.8)	55 (52.9)	0.472			
Transplant	11 (3.5)	8 (3.8)	3 (2.9)	1			
Malignancy	10 (3.2)	7 (3.3)	3 (2.9)	1			
Hypothyroid	17 (5.4)	8 (3.8)	9 (8.7)	0.109			
Rheumatology	3 (1.0)	1 (0.5)	2 (1.9)	0.257			
Others	47 (15.0)	22 (10.5)	25 (24.0)	0.002			

Table 2: Incidence & Microbiology of MDROs among COVID-19 patients.

Outcome		Discharged n, %		Died n, %		Total n, %
MDRO status	Colonized	30 (68.2%)		14 (31.8%		44 (100%)
	Infection	30 (50%)		30 (50%)		60 (100%)
MDRO Name	MDRO1	MDRO2	MDRO3	Total	Percent	
ESBL	39	6	1	46	34.1	
CRE	21	10	2	33	24.4	
MDRA	14	3	0	17	12.6	
MDRPs	4	2	0	6	3.7	
MRSA	18	3	0	21	15.6	
VRE	4	3	0	7	5.2	
C. auris	4	0	1	5	3.7	
Total	104	27	4	135		
Infection versus colonization	Colonization (n, %)		Infection (n, %)			
	47 (34.8%)		88 (65.2%)			
Time of detection	Detected with 48 hours (n, %)		Detected after 48 hours (n, %)			
	42 (31.1)		93 (68.9)			
RH Acquired, other hospital Acquired, community Acquired	RH Acquired n, (%)		Other Hospital Acquired n, (%)		Community Acquired n, (%)	
	93 (68.9)		33 (24.4)		9 (6.7) (5 MRSA, 4 ESBL)	

Month	Total Adm critical	Total Adm Ambulatory	Total Adm COVID-19	Total patient days critical	Total pts days Ambulatory	Total patient days	Total MDRO	Inci/ 1000 patient days	Inci /100 Adm
Apr	18	4	22	176	100	276	3	10.9	13.6
May	27	40	67	506	372	878	8	9.1	11.9
Jun	67	133	200	1001	812	1813	14	7	7.5
Jul	54	145	199	1300	1081	2381	38	16	19.1
Aug	32	75	107	927	509	1436	33	22.9	30.8
Sep	47	112	159	875	401	1276	39	30.6	20
Total	245	508	753	4785	3275	8060	135	16.7	17.9

	ESBL Acquired	ESBL Inci/1000	CRE Acquired	CRE Inci/1000	MDRA Acquired	MDRA Inci/1000	MDRPs. Acquired	MDRPs Inci/1000	MRSA Acquired	MRSA Inci/1000	VRE Acquired	VRE Inci/1000	C. auris Acquired	C. auris Inc/1000
Apr	2		1		0		0		0				0	
May	4		0		0		1		3				0	
Jun	6		1		0		1		6				0	
Jul	14		8		8		1		6				1	
Aug	10		15		1		2		1		4		0	
Sep	10		8		8		1		5		3		4	
Total	46	5.7	33	4.1	17	2.1	6	0.7	21	2.6	7	0.9	5	0.6

\MDRO1: case acquired 1 MDRO, MDRO2: case acquired 2 MDRO, MDRO3: case acquired 3 MDRO, Adm: Admission, Inci: incidence, RH: Royal Hospital

Table 3: Determinants of mortality among MDROs positive C0VID-19 patients.

Variables	Total (n=104)	Infected (n=60)	Colonization (n=44)	p-Value	Multi-variate logistic regression		
	n (%)	n (%)	n (%)		Adjusted odds ratio	95% C.I.	p-Value
Gender							
Male	69 (66.3)	40 (66.7)	29 (65.9)	1.000			
Female	35 (33.7)	20 (33.3)	15 (34.1)				
Admission							
Direct	44 (42.3)	28 (46.7)	16 (36.4)	0.321			
Transferred	60 (57.7)	32 (53.3)	28 (63.6)				
ICU admission							
Yes	95 (91.3)	56 (93.3)	39 (88.6)	0.489			
No	9 (8.7)	4 (9.7)	5 (11.4)				
Ventilators							
Yes	87 (83.7)	52 (86.7)	35 (79.5)	0.423			
No	17 (16.3)	8 (13.3)	9 (20.5)				
Tracheostomy							
Yes	40 (38.5)	29 (48.3)	11 (25.0)	0.024	1.54	0.53 – 4.46	0.432
No	64 (61.5)	31 (51.7)	33 (75.0)				
NGT							
Yes	87 (83.7)	53 (88.3)	34 (77.3)	0.18			
No	17 (16.3)	7 (11.7)	10 (22.7)				
Pronning							
Yes	65 (62.5)	41 (68.3)	24 (54.5)	0.159			
No	39 (37.5)	19 (31.7)	20 (45.5)				
Antibiotics							
<4	64 (61.5)	29 (48.3)	35 (79.5)	0.002	3.09	1.13 – 8.44	0.028

≥4	40 (38.5)	31 (51.7)	9 (20.5)				
Acute dialysis							
Yes	19 (18.4)	13 (22.0)	6 (13.6)	0.315			
No	84 (81.6)	46 (78.0)	38 (86.4)				
Age		58.17±14.63	55.91±15.64	0.452			
Length of hospital stay		35.69±22.32	21.16±16.55	<0.001*	1.03	0.98 – 1.07	0.231
Length of ICU stay		23.62±13.89	16.49±11.75	0.009*	0.99	0.94 – 1.05	0.862

*Mann-Whitney test

Table 4: Clinical characteristics by group and logistic regression for the mortality.

Variables		Total (n=313)	Discharged (n=196)	Died (n=117)	p-Value	Multi-variate logistic regression		
		n (%)	n (%)	n (%)		Adjusted odds ratio	95% C.I.	p-Value
	Control	209 (66.8)	136 (69.4)	73 (62.4)	0.217			
	Case	104 (33.2)	60 (30.6)	44 (37.6)				
Age		55.70±16.03	50.32±15.78	64.71±11.89	<0.001	1.087	1.06-1.11	<0.001
Male		218 (69.6)	137 (69.9)	81 (69.2)	0.9			
	0	209 (66.8)	136 (69.4)	73 (62.4)	0.549			
	1	77 (24.6)	46 (23.5)	31 (26.5)				
	2	23 (7.3)	12 (6.1)	11 (9.4)				
	3	4 (1.3)	2 (1.0)	2 (1.7)				
Length of ICU stay		11 (5, 19)	9 (5, 20)	12 (7, 18.5)	0.045	0.989	0.96-1.02	0.518
Invasive Devices	Ventilation	225 (71.9)	118 (60.2)	107 (91.5)	<0.001	2.576	0.42-15.76	0.306
	Central Line	240 (76.7)	132 (67.3)	108 (92.3)	<0.001	1.303	0.34-4.97	0.699
	Urinary catheter	230 (73.5)	124 (63.3)	106 (90.6)	<0.001	0.592	0.15-2.42	0.466
	Tracheostomy	58 (18.5)	30 (15.3)	28 (23.9)	0.071	0.676	0.26-1.73	0.413
	Nasogastric Tube	225 (71.9)	117 (59.7)	108 (92.3)	<0.001	2.826	0.56-14.39	0.211
Pronning		151 (48.2)	85 (43.4)	66 (56.4)	0.027	1.412	0.69-2.88	0.342
	1	37 (24.5)	20 (23.5)	17 (25.8)	0.644			
	2	45 (29.8)	30 (35.3)	15 (22.7)				
	3	39 (25.8)	20 (23.5)	19 (28.8)				
	4	19 (12.6)	10 (11.8)	9 (13.6)				
	5	8 (5.3)	4 (4.7)	4 (6.1)				
	6	3 (2.0)	1 (1.2)	2 (3.0)				
Acute dialysis		46 (14.7)	13 (6.6)	33 (28.4)	<0.001	4.392	1.82-10.61	0.001

Discussion

The first two COVID-19 cases in Oman, diagnosed on 23 February 2020, were linked to travel history to the Islamic Republic of Iran. (6). From April 2020, confirmed cases started to be admitted to our hospital. An operational preparedness plan was prepared ahead of this, which included enhanced infection prevention and control strategies for COVID-19 admissions. Our study showed that the independent factors for mortality among this cohort are age and acute dialysis, which indicates that the severe disease cases of COVID-19 are dying early; however, MDRO acquisition was not associated with the worse outcome as it was addressed by Karruli et al. [5]. Risk factors for acquisition of MDROs in addition to the length of ICU stay, length of hospital stay, was the presence of invasive devices (ventilation, tracheostomy, NGT, central lines, urinary catheters), receiving multiple antibiotics and pronning which indicate the acuity of the cases and more nursing care is delivered to such patients. Other studies confirmed this [7]. Pronning of ventilated COVID-19 patients done for all patients who had no contraindications, the practice that requires at least 6-8 staff to accomplish this procedure. Hence other staff caring for patients colonized or infected with MDROs who might not have changed their top gown or did not practice hand hygiene properly assist in such procedure. In addition, as described in other studies, HCWs focused on self-protection rather than preventing cross-transmission [8]. Not surprisingly, co-morbidities came as an independent risk factor for MDRO acquisition among the study cohort as these patients will stay longer in the hospital, have more antibiotics, and have more exposure to other MDROs patients.

The commonest MDRO was ESBLs in our study, which were not part of the active MDRO surveillance and were detected from clinical samples. CRE and MDRA were the next commonest MDROs detected. By the end of the first wave, VRE and C. auris started to appear. The changes in the MDROs detected de-

pend on the local epidemiology of the center and vary greatly across centers and countries [5,7,9].

The study showed that as the surge capacity progressed, more patients were admitted to critical COVID-19 wards in our hospital, leading to more MDRO acquisitions. A severe shortage of experienced critical care staff and more deployment of inexperienced staff accompanied this. In addition, the interruption of chain supplies included PPE, patient care items such as Catheter types, skin and environmental disinfection items and solutions that might have contributed to the cross-transmission among these patients during the study period.

The study confirmed that mortality was significantly higher among patients who developed hospital-acquired infections than those who remained colonized, as discussed by other studies. This highlight the need to implement infection prevention bundles among high-acuity patients to prevent infection is pivotal. The provision of experienced critical care staff who are trained in infection prevention and control is essential but is usually difficult to implement in a surge capacity, as was experienced in the pandemic.

One strength of this study is the good sample size with various MDROs of concern. In addition, it studied the effect of pronning of ventilated patients as a risk factor for the acquisition of MDROs among COVID-19.

This study has a few limitations. First, it is a single centre and retrospective. We could not include all patients admitted with COVID-19 as not all of them were screened on admission. The hospital MDRO surveillance was not continuous such as once weekly, and all patients were to be screened; hence, we might have missed cases. We did not study the appropriateness of the use of antibiotics. Also, we did not study the effect of other medications, such as steroids or tocilizumab, on the acquisition of MDROs.

Conclusion

The acquisition of MDROs was not associated with worse outcomes among COVID-19 patients, although mortality was significantly higher among infected patients than colonized patients. Implementing strict infection prevention and control strategies is vital to prevent colonization and progression to infection among colonized patients.

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