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Original Article

Risk of invasive MDRO infection in MDRO-colonized patients

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Abstract

Objective: In this study, we aim to estimate the risk of developing clinical multidrug-resistant organism (MDRO) infection with carbapenem-resistant *Enterobacterales* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), or vancomycin-resistant enterococci (VRE) in colonized patients compared with non-colonized admitted to high-risk areas with a main focus on CRE colonization/infection.

Design and setting: Retrospective cohort study conducted at a tertiary care facility.

Methods: This study included patients enrolled in active surveillance testing (AST) for CRE, MRSA, or VRE during the year 2021. Development of relevant invasive infection within 365 days of the AST result was collected as the primary outcome. The association between MDRO colonization and infection was calculated using the risk ratio. The prevalence of CRE organisms and carbapenemase genes is presented.

Results: A total of 19,134 ASTs were included in the analysis (4,919 CRE AST, 8,303 MRSA AST, and 5,912 VRE AST). Patient demographics were similar between colonized and non-colonized groups. Colonization was associated with an increased risk of infection in the 3 cohorts (CRE, MRSA, and VRE), with risk ratios reported as 4.6, 8.2, and 22, respectively. Most patients (88%) develop CRE infection with the same colonizing carbapenemase gene. Oxa-48/NDM *Klebsiella pneumoniae* was the most common organism detected in CRE infection.

Conclusions: The study demonstrated that colonization with CRE, MRSA, or VRE is a risk factor for developing infections caused by the respective bacteria. The high percentage of match between carbapenemase genes detected in colonization and infection indicates that screening results might be used to inform infection management and treatment.

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Introduction

The prevalence of multidrug-resistant organisms (MDROs) colonization varies across pathogens and continents.[1] According to a pooled estimate of studies conducted between 1987 and 2020 (n = 15), Asia reported the highest prevalence of carbapenem-resistant Enterobacterales (CRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, while vancomycin-resistant enterococci (VRE) colonization was found to be 0.[1] Colonization with MDRO was associated with an increased incidence of subsequent MDRO infection. A systematic review found that 7.6%–44.4% of 1,806 CRE-colonized patients developed clinical CRE infections.[2] Colonization with MRSA or VRE increased the risk of related infection by 2.7–3.6 (RR) and 14.3 (OR), respectively.[3,4] Surveillance strategies were therefore developed to monitor MDRO colonization and have been considered crucial for preventing and controlling the further spread of MDRO organisms in healthcare facilities.[5–7] Although it has been established that prior MDRO colonization correlates with an increased risk of subsequent infection, little is known about the prevalence of MDRO colonization in Saudi Arabia's healthcare facilities and the extent to which this association is observed. Knowing that Saudi Arabia is a possible endemic country for MDRO,[8] more efforts are needed to understand the current status of MDRO infection and its relationships with other relevant factors. Therefore, this study aims to estimate the risk of developing MDRO infections in colonized patients compared with non-colonized individuals admitted to high-risk areas at a tertiary care hospital in Saudi Arabia in 2021, with a specific emphasis on CRE status and the prevalence of carbapenemase genes.

Methods

Study setting and population

This retrospective cohort study was conducted at King Faisal Specialist Hospital and Research Center (KFSHRC), a tertiary healthcare facility located in Riyadh, Saudi Arabia, which provides specialized medical care with around 960 active beds. KFSHRC established an active surveillance testing (AST) routine that screens for CRE, MRSA, and VRE colonization upon admission to or transfer to high-risk areas if the transfer occurs after day 7 of

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admission. A detailed explanation of the AST implemented in KFSHRC is presented in Supplementary Table 1. Upon positive results of AST, contact precautions are automatically generated into patients' electronic medical records. Typically, patients will remain in isolation during subsequent admissions until cleared by infection control practitioners, based on risk assessment and discontinuation criteria (Supplementary Table 2). The isolation status will be automatically displayed during the readmission process. MDRO decolonization is considered only for MRSA patients under specific criteria (Supplementary Table 3). All rooms in our facility are single rooms, except for 2 units. In the case of double-bed rooms, our policy stipulates that patients colonized with a specific MDRO should be placed in cohort isolation with patients colonized with the same organism. Patient charts that indicate enrollment in the AST during 2021 were identified and included in this study. In cases of multiple tests, only the positive AST was considered. If all tests were negative, only the first negative AST was included. Tests were also excluded if the specimen was purified colony or the results were invalid. Tests with colony specimens are not AST; instead, they represent further analysis of a clinical infection. The study group was colonized patients defined as those testing positive with CRE, VRE, or MRSA detected from rectal/perirectal swabs in (VRE and CRE) or nasal/skin swabs in MRSA, with no signs and symptoms of infection. The control group was patients with negative results on AST (non-colonized). The study was approved by the KFSHRC ethics committee, which waived the need for informed consent.

Study variables

The included patients were divided into 3 cohorts based on the type of AST performed (CRE, MRSA, VRE). Patients with more than one AST, for example, CRE AST and VRE AST, were included in all relevant cohorts. Data were collected on age, gender, and AST results. For the CRE cohort, additional data on carbapenemase gene results were collected.

Study outcomes

The primary outcome was the occurrence of invasive infection relevant to the colonizing organism within 365 days of the AST date. A relevant infection was identified if blood, urine, or cerebrospinal fluid culture tested positive for CRE, MRSA, or VRE organisms. Other sources of infection, such as tracheal aspirate and wound, are non-sterile specimens and well-known colonization sites and, therefore, need to correlate with multiple factors before being considered infections, which is beyond the scope of this study. As a result, patients with positive tracheal aspirate and wound cultures were not counted in the outcome of subsequent infection.

Microbiological methods

All surveillance culture swabs, including nasal and skin for MRSA, and rectal swabs for VRE and carbapenemase screening, are done on the GeneXpert® System following the manufacturer's recommendations. All isolates from clinical samples, once they grow on culture media, are identified by VITEK® MS bioMérieux, an automated mass spectrometry microbial identification system that uses Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology. Antimicrobial susceptibility testing is performed on the VITEK 2 system. All antibiotics minimum inhibitory concentration (MIC) breakpoints are reported following the Clinical Laboratory Standard Institute (CLSI) interpretation guidelines or the European Clinical Antibiotics Susceptibility Testing (EUCAST) interpretation if CLSI is not available.

Statistical analysis

The two groups' characteristics were presented using summary statistics, such as mean ± SD or median [IQR] for continuous variables and frequencies/proportions for categorical variables. χ^2 or Fisher's exact test (categorical variables) and *t* test or Mann-Whitney test (continuous variables) were used for group comparison as appropriate. The risk ratio and its 95% confidence interval are used to measure the association between colonization and subsequent infection.

Results

In the current study, 32,037 active surveillance tests were performed in 2021, with only 19,134 ASTs included in the analysis, classified as CRE AST (n = 4919), MRSA AST (n = 8303), and VRE AST (n = 5912) (Figure 1).

Demographic data of the three cohorts are presented in Table 1. Among the cohort screened for CRE, 445 (9%) had a detectable carbapenemase gene (ie, were considered colonized). The distribution of positive genes was as follows: Oxa-48 (269 patients), NDM (231 patients), VIM (36 patients), KPC (21 patients), and IMP (10 patients). It is important to note that some patients tested positive for more than one gene. For participants in MRSA AST, 10% were colonized with a mean age of 38 years. Among those tested for VRE, 14% were colonized. Most colonized individuals in the 3 cohorts were male, representing a percentage between 52% and 54%. CRE-colonized and VRE-colonized patients were older than non-colonized, though the difference was not significant.

In the CRE cohort, there were more events of bacterial infections caused by gram-negative bacteria (GNB) in the colonized group compared with non-colonized (31% vs 20.3%), with a risk ratio of 1.5 (95% CI, 1.3–1.8), suggesting a higher risk of GNB infection among CRE colonizers (Table 2). Similar results were observed with infections caused by Enterobacterales. Infections with CRE were also more prevalent in the CRE-colonized group (10%) compared with non-colonized patients (2%), making CRE carrier patients 4.6 times more likely to develop CRE infection (95% CI, 3.3–6.4). Most CRE were isolated from blood in the colonized group, while urine was the most common site of infection in the non-colonized group.

In Table 3, the characteristics of CRE infections were examined in patients who had undergone CRE AST, comparing CRE colonized and non-colonized. Among the 46 patients with phenotypic CRE infection in the colonized group, a large proportion (57%) had additional molecular testing to identify the carbapenemase gene, with 88% yielding positive results. In contrast, additional molecular testing was performed less frequently in the non-colonized patients with CRE infection (29%), and carbapenemase genes were detected in 45% of these cases. The NDM gene was most prevalent in the CRE-colonized group, primarily associated with *Klebsiella pneumoniae*. The Oxa-48 gene was also common in both groups and mainly detected in *Klebsiella pneumoniae*. Further analysis revealed that 88% of patients who underwent additional molecular testing for CRE infection had the same carbapenemase genes detected during AST.

In the MRSA-colonized group, 23 patients (2.8%) experienced MRSA infections compared with 26 patients (0.3%) in the

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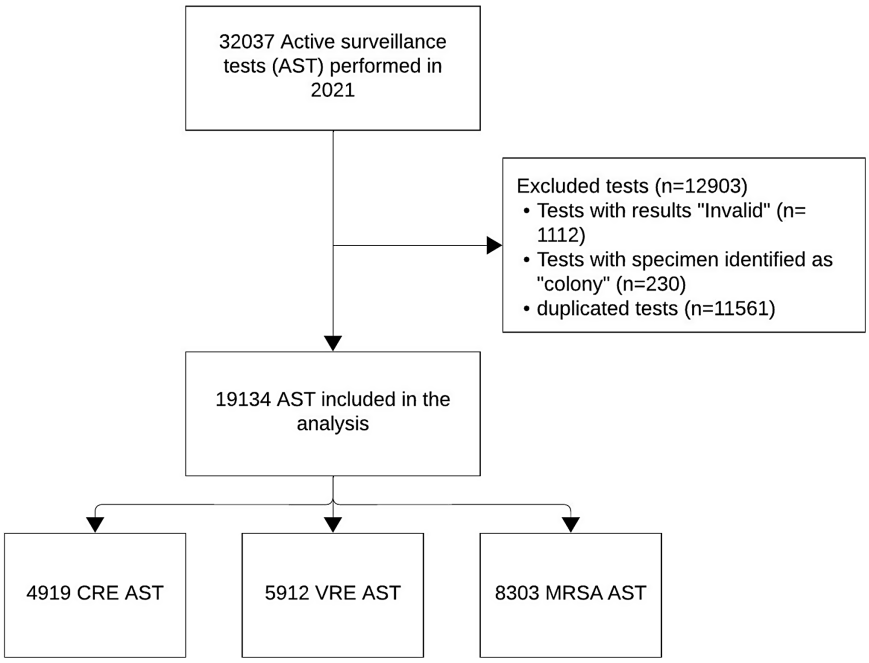

Figure 1. Flowchart of inclusion and exclusion criteria of the study sample.

non-colonized group. The MRSA-colonized group was 8.2 times more likely to develop subsequent invasive MRSA infection. The most common site of MRSA infection was blood in both groups (Table 4).

The VRE-colonized group had a significantly higher risk of developing subsequent VRE infection, with a risk ratio of 22 (95% CI, 10.1–48.1). Contrary to MRSA infection, most VRE infection was reported from urine specimens in colonized (53%) and non-colonized (62%) groups (Table 4). The median time from AST to clinical infection was reduced for patients colonized with CRE and VRE. In contrast, MRSA-colonized patients took longer to develop a clinical MRSA infection compared with non-colonized patients, though the difference was not significant (Supplementary Table 4).

Discussion

The results of this study indicate that the presence of MDRO colonization is associated with an increased risk of subsequent MDRO infection, with the highest risk of relevant infection observed in the vancomycin-resistant *Enterococcus* colonized group.

MDRO infections present a significant challenge in healthcare environments.[9,10] MRSA and VRE were classified as serious threats in the Centers for Disease Control and Prevention's 2019 antibiotic resistance report due to their clinical impact and the ongoing threat of treatment limitation.[11] In our study, 10% and 14 % of patients were colonized with MRSA and VRE, respectively, which poses significant challenges in controlling their spread. The risk of subsequent infection increased among MRSA and VRE-colonized patients, with the highest incidence observed in the VRE group. One possible explanation comes from a study by Ubeda et al, which revealed that once VRE invaded the body, they became the dominant species in the gut microbiome of mice following antibiotic treatment, comprising over 95% of the gut microbiome.[12] This dominance persisted for 7 days after antibiotic cessation and preceded bloodstream infection in humans, particularly in hematopoietic stem cell transplantation (HSCT) patients.[12] The generalizability of these findings to all VRE-colonized patients is unknown, but our sample might pose certain risk factors, such as frequent use of antibiotics and chemotherapy, which could contribute to VRE proliferation and the disturbance of the gut mucosa, thereby increasing the likelihood of VRE translocating to extra-intestinal organs. This study's findings indicate that infection control strategies toward persons who have been identified as carriers of MDROs should be maintained and enhanced to mitigate the occurrence and transmission of MDROs infections.

An increase in the prevalence of multidrug-resistant gram-negative bacteria has been reported worldwide.[13–16] Gram-negative resistance to carbapenem is particularly concerning due to its association with complicated infection and high mortality.[17] Our results found 9% colonization with carbapenemase-producing organism (CRE), which amplified the likelihood of future CRE infection by 360% (risk ratio 4.6) as supported by previous literature.[2,18] Patients colonized with CRE were at a higher risk of developing bloodstream infections compared with non-colonized individuals, who showed a higher incidence of urinary tract infections. This suggests that patients with CRE colonization were more susceptible to serious infections, although there is conflicting evidence in the literature.[19,20]

Our investigations also showed that CRE-colonized patients are more likely to undergo molecular testing (59%) when subsequent clinical CRE infection develops compared with non-colonized individuals (21%). Molecular techniques help to attain a more exhaustive comprehension of CRE infections by identifying the precise carbapenemase genes linked to the isolates. One notable discovery in our research was the agreement shown between the carbapenemase genes identified in CRE-colonized patients and those present in later clinical infections. In the cohort of individuals colonized with CRE, it was observed that 88% of the colonized group who underwent molecular testing exhibited CRE infections with identical carbapenemase genes as those identified during colonization. This observation implies the possibility of a continued presence of CRE strains from the initial colonization stage through subsequent infection in these particular patients. The

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Table 1. Patient characteristics of the 3cohorts under study

Patient characteristics	Colonized	Non-colonized	*P* value
CRE n=4919			
N (%)	445 (9)	4474 (91)	
Age mean (SD)	51.2 (19.3)	49.5 (19.4)	.07
Sex (female)	206 (46)	2172 (49)	.4
Colonizing carbapenemase gene	567*	–	
Oxa-48	269 (47)	–	
NDM	231 (41)	–	
VIM	36 (6)	–	
PC	21 (4)	–	
MP	10 (2)	–	
MRSA n=8303			
N (%)	809 (10)	7494 (90)	
Age mean (SD)	38.4 (26.4)	41.2 (25)	.003
Sex (female)	386 (48)	3528 (47)	.8
VRE n=5912			
N (%)	834 (14)	5078 (86)	
Age mean (SD)	43 (25.5)	40.1 (24.8)	.002
Sex (female)	388 (47)	2406 (47)	.6

Data presented as n (%).
CRE, carbapenem-resistant *Enterobacterales*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
*Some patients are positive with more than one gene.

Table 2. Bacterial infection events in patient with CRE active surveillance testing results

Variable	Colonized (445)	Non-colonized (4474)	*P* value	Risk ratio (95% CI)
Infection with GNB	138 (31)	908 (20.3)	<.001	1.5 (1.3–1.8)
Infection with Enterobacterales	111 (30)	746 (16.7)	<.001	1.5 (1.3–1.8)
CRE infection	46* (10.3)	68* (1.5)	<.001	4.6 (3.3–6.4)
Blood	30 (7)	26 (1)	<.01	
Urine	18 (4)	44 (1)	<.01	
CSF	0	2 (<1)	–	

Data presented as n (%).
CRE, carbapenem-resistant Enterobacterales; GNB, gram-negative bacteria; CSF, cerebrospinal fluid.
*Patient with multiple CRE infection is counted once in number of infection, but if the source is different (blood/urine), they will be included in each source of infection.

Table 3. Characteristics of CRE infection in patients with CRE active surveillance testing results

Variable	Colonized (445)	Non-colonized (4474)
Phenotypical CRE infection	46 (10.3)	68 (1.5)
Klebsiella pneumoniae	30 (65)	17 (25)
Pseudomonas aeruginosa	6 (13)	29 (43)
Escherichia coli	7 (15)	5 (7)
Enterobacter cloacae	2 (4)	4 (6)
Pseudomonas putida	0	1 (1)
Citrobacter species	0	3 (4)
Ralstonia mannitolilytica	0	3 (4)
Klebsiella species	1 (2)	0
Proteus mirabilis	0	2 (3)
Salmonella	0	1 (1)
Serratia	0	2 (2)
Shigella species	0	1 (1)
Cultures with additional molecular testing	26 (57)	20 (29)
Cultures with carbapenemase gene detected	23 (88)	9 (45)
Oxa-48	12 (50)	6 (66.7)
Klebsiella pneumoniae	11 (92)	6 (100)
Escherichia coli	1 (8)	
NDM	13 (50)	3 (33.3)
Klebsiella pneumoniae	8 (66.7)	
Escherichia coli	2 (16.7)	
Enterobacter cloacae	2 (16.7)	1 (33.3)
Pseudomonas aeruginosa	1	
Citrobacter freundii	–	1 (33.3)
Serratia marcescens	–	1 (33.3)
KPC	2 (8.3)	1 (1.1)
Klebsiella pneumoniae	2 (100)	1 (100)
VIM	0	0
IMP	0	0
Infection with at least one carbapenemase gene identical to the colonizing gene	23 (88)	

Data presented as n (%).
CRE, carbapenem-resistant Enterobacterales.

prevalence of carbapenemase genes exhibited variability, along with their connection to specific organisms. The most prevalent carbapenemase genes identified in the CRE-colonized group in our study were Oxa-48 and NDM, with a particular association shown with *Klebsiella pneumoniae*. These findings are consistent with previous studies.[21–23] The provided information has the potential to enhance empirical treatment decisions, facilitating the prompt initiation of suitable therapy and potentially improving patient outcomes. The detection of specific carbapenemase genes linked to infections can have significant implications for the practice of antimicrobial stewardship.[24] Understanding the predominant causes of resistance helps inform the choice of appropriate antibiotics and minimize the use of ineffective drugs.

Our study has some limitations. Initially, the study was conducted within a specific hospital environment, and the sample was selected based on surveillance tests applied only in critical care settings, hence limiting the direct generalizability of the findings to other settings characterized by different patient demographics and infection control protocols. Additionally, our risk ratio might be overestimated, considering that colonized patients are prone to increased length of stays, ventilator days, and rehospitalization rates,[25–27] which in return might increase the risk of infection. Due to time and budget constraints, it was not possible to collect data on other factors that could further influence the outcome; however,

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Table 4. MRSA and VRE bacterial infection events in colonized and non-colonized groups

Variable	Colonized	Non-colonized	*P* value	Risk ratio (95% CI)
Infection with MRSA	23* (2.8)	26 (0.3)	<.001	8.2 (4.7–14.3)
Blood	23 (2.8)	19 (0.3)	<.001	
Urine	1 (0.1)	6 (0.1)	.5	
Infection with VRE	29* (3.5)	8 (0.2)	<.001	22.1 (10.1–48.1)
Blood	15 (1.8)	3 (0.1)	<.001	
Urine	17 (2)	5 (0.1)	<.001	

Data presented as n (%).
MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
*Patient with multiple MRSA or VRE infections is counted once in number of infection, but if the source is different (blood/urine), they are included in each source of infection.

previous literature that controlled for multiple factors has shown that colonization independently increases the odds of subsequent infection.[3,28]

In conclusion, our research underscores the need to implement AST for MDRO colonization to identify patients who are at a heightened risk of developing MDRO infections. The high percentage of agreement between carbapenemase genes identified in colonization and infection suggests a long-term survival of CRE strains. This emphasizes the need of implementing rigorous infection control measures to effectively mitigate transmission.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2024.156.

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Competing interests. None.

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