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ORIGINAL RESEARCH

From Colonisation to Infection: Assessing the BSI Potential in Patients with KPC, NDM, VRE and CRAB Rectal Colonisation

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ABSTRACT

***Introduction*:** Multi-drug-resistant organisms (MDROs) that mostly contribute to nosocomial infections include carbapenem-resistant Enterobacterales that produce Klebsiella pneumoniae carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and vancomycin-resistant *Enterococcus faecium* (VRE). Patients colonised by these MDROs are at high risk for developing bloodstream infections (BSIs) by the same pathogen, emphasising the need for surveillance and intervention.

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Methods: This retrospective study included patients admitted to medical, surgical, and intensive care unit (ICU) wards in the IRCCS Policlinico San Matteo (Pavia, Italy) between January 2019 and October 2024 with rectal colonisation by KPC, NDM, VRE and CRAB. Demographic, clinical and microbiological data were extracted from electronic records. Logistic regression with stepwise model-building identified risk factors for BSI development.

Results: A total of 1969 patients colonised with MDRO were identified: 79% of them were colonised by KPC, VRE, CRAB or NDM. Among the 1960 hospitalisations involving these specific rectal colonisations, the overall rate of BSIs was 9.4%, with CRAB and KPC showing the highest rates (20.0% and 12.6%, respectively). ICU hospitalisation was significantly associated with an increased risk of BSI in patients colonised with KPC, NDM and VRE. Haematological malignancies and bone marrow transplantation were independent risk factors for BSI in patients colonised with KPC (odds ratio [OR] = 3.22, $p = 0.037$) and VRE (OR = 4.07, $p = 0.004$) whereas solid organ transplantation increased BSI risk among patients colonised with CRAB (OR = 11.83, $p = 0.034$).

Conclusions: Our findings show heterogeneous BSI risk among MDROs, with CRAB and KPC being the most dangerous, especially in patients in the ICU, followed by VRE in onco-haematological cases. These results support developing prevention strategies for critically ill and immunocompromised patients.

Keywords: Multi-drug-resistant organisms; Rectal colonisation; Bloodstream infections; Risk factors; Logistic regression

Key Summary Points

Bloodstream infections (BSIs) caused by multi-drug-resistant organisms (MDROs) represent a major clinical threat, especially in intensive care units (ICU) and immunocompromised patients.

The progression from rectal colonisation to BSI is variable and understudied across different MDROs (KPC, NDM, VRE and CRAB).

This study aimed to estimate the incidence of BSIs and identify risk factors for BSI development in rectally colonised patients.

Among 1960 colonised hospitalisations, BSI occurred in 9.4% of cases, with the highest rates for CRAB (20.0%) and KPC (12.6%). ICU stay increased BSI risk for KPC, NDM and VRE; haematologic malignancies and bone marrow transplant for KPC and VRE; and solid organ transplant for CRAB.

The risk of BSI significantly varies depending on the colonising MDRO and patient clinical profile, highlighting the need for stratified surveillance and empiric treatment strategies in high-risk populations.

INTRODUCTION

The main multi-drug-resistant organisms (MDROs) implicated in nosocomial infections worldwide are carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), vancomycin-resistant *Enterococcus faecium* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. According to estimates by the European Centre for Disease Prevention and Control (ECDC), Italy shows concerning levels of antimicrobial

resistance (AMR), with approximately 26% of *Klebsiella pneumoniae* isolates and 76% of *Acinetobacter baumannii* isolates resistant to carbapenems and 32.5% of *E. faecium* isolates resistant to vancomycin [2].

A common surveillance strategy for MDROs involves screening with rectal swabs to detect intestinal colonisation by CRE, CRAB and VRE [3]. This is particularly important given the well-documented risk of colonised patients developing systemic infections, especially bloodstream infections (BSIs), caused by the same colonising organism [4, 5]. Understanding the prevalence of infection among patients with rectal colonisation by different MDROs and identifying key risk factors are crucial to guide clinicians in selecting appropriate empirical antibiotic therapy [6]. This approach would allow for the prompt initiation of effective treatment in high-risk patients, while avoiding the indiscriminate use of broad-spectrum antibiotics in low-risk cases.

To address these challenges and given the clinical impact of MDRO infections in the Italian setting, we conducted a *real-life* study in a large University Centre in Northern Italy, including all colonised patients, to assess the risk of BSI development. Unlike previous studies that focused on specific high-risk populations and pathogens, our study evaluated the infection risk in a broader, more representative patient cohort, comparing the progression to BSI across different MDROs. The primary objective was to determine the rate of BSI in patients with different types of rectal colonisation, while the secondary objectives were (i) to identify the patients' underlying conditions associated with BSI development for each colonising MDRO and (ii) to determine which MDRO colonisation was most likely to progress to BSI.

METHODS

Study Design

This was a retrospective, single-centre, observational study conducted at the IRCCS Policlinico San Matteo in Pavia, Northern Italy, from January 2019 to October 2024.

Study Population

The study included patients with rectal colonisation by multi-drug-resistant organisms (MDROs). However, for the final analysis, only Klebsiella pneumoniae carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM)-producing *Klebsiella pneumoniae*, vancomycin-resistant *Enterococcus faecium* (VRE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) were considered.

Other MDROs were excluded owing to low colonisation rates or low incidence of BSIs in colonised patients.

Some patients experienced multiple hospitalisations and were colonised by more than one MDRO. Since comorbidities and colonisation status changed across hospitalisations, analyses were performed at the hospitalisation level to allow for a more accurate reflection of the burden of disease.

Study Setting

The IRCCS Policlinico San Matteo is a tertiary-care teaching hospital with a wide range of wards, including intensive care units (ICUs), haematology, surgical and medical wards.

During the study period, the patients admitted to ICU and haematology wards were screened for MDRO carriage on admission and weekly by rectal swab. Conversely, in other medical and surgical wards, screening has been performed only in high-risk patients, such as those transferred from long-term care facilities or other hospitals.

Data Collection and Variables

Clinical and microbiological data were retrieved from electronic health records. The following variables were recorded: (i) demographics (age and biological sex), (ii) comorbidities such as cardiovascular diseases, hypertension, diabetes, obstructive pulmonary diseases, chronic kidney

diseases, chronic liver diseases, rheumatic diseases, neoplasia, solid organ transplant (SOT), neutropenia, haematological malignancies and bone marrow transplant (BMT), (iii) microbiological data, namely MDRO colonisation status, infection and antimicrobial susceptibility testing (AST) and (iv) clinical outcomes, such as development of BSI, length of stay (LOS) and intrahospital mortality.

Data Management

Data were retrieved from the hospital's data platform, integrating multiple sources: (i) admission/discharge/transfer (ADT) system: demographic data, hospital admission/discharge details and ward of stay as well as (ii) laboratory information system (LIS): microbiological data, including rectal swabs and blood culture (BC) results. A relational database (Oracle SQL) was used to integrate data from rectal swabs and BCs. All data were anonymised in compliance with data protection regulations.

Definitions

MDRO colonisation was defined as a positive rectal swab for KPC, VRE, CRAB or NDM, while BSI was defined as a positive BC for the same MDRO previously identified in rectal swabs. The same MDRO was defined as the same species and resistance pattern, without molecular identification.

Specifically, BSIs were identified by matching positive BCs with rectal swab results from the same patient within a defined timeframe, namely from 7 days before the swab until hospital discharge. Cases with missing microbiological data were excluded.

Hospital wards were grouped into three categories: (i) ICU, (ii) surgical departments: general surgery, vascular surgery, thoracic surgery, orthopaedics, neurosurgery, otolaryngology, gynaecology and urology and (iii) medical departments: internal medicine, cardiology, pulmonology, nephrology, oncology, haematology, infectious diseases, neurology and geriatrics.

Metabolic syndrome was defined as the presence of diabetes, hypertension or cardiovascular diseases.

Microbiological Methods

Rectal swabs were processed on selective chromogenic media (CHROMID® CARBA, CHROMID® ESBL, CHROMID® VRE bioMérieux, Marcy-l'Etoile France) and incubated at 35–37 °C for 18–48 h. Colony identification was performed by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany) and analysed using the BioTyper version 3.1. Carbapenemase production was confirmed using the NG-Test® CARBA-5 immunoassay (NG Biotech Laboratories, Guipry, France) or the molecular-based test (Xpert Carba-R kit, Cepheid, Sunnyvale, CA, USA). The first isolate was subjected to antimicrobial susceptibility testing (AST) using the BD Phoenix 50™ instrument (Becton Dickinson, Franklin Lakes, NJ, USA). Minimum inhibitory concentration (MIC) values were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST). BCs were incubated into the BD BACTEC FX system, positive blood culture bottles were subjected to Gram staining, subculturing, species identification and antimicrobial susceptibility testing (AST) according to laboratory procedures.

Statistics

Continuous variables were reported as median and interquartile range (IQR), while categorical variables were represented with absolute frequencies and percentages. Logistic regression models were used to assess the association between demographic, clinical and ward factors and the probability of BSI in patients with rectal MDRO colonisation. Starting from the full model (age, sex, ward, metabolic syndrome, obstructive pulmonary diseases, chronic kidney diseases, chronic liver diseases, rheumatic diseases, neoplasia, SOT, oncohaematology and BMT), a stepwise model-building approach was

applied for covariate selection, where predictors were sequentially removed on the basis of their contribution to minimising the Akaike information criterion (AIC). Statistical analyses were conducted using the *stepAIC* function (MASS toolbox) in R (version 4.2.1), and statistical significance was set at p-values < 0.05.

Additionally, further analyses were performed on 'prototypic patients'. Specifically, for each pathogen and mechanism, we used the estimated model to identify the 'most favourable' and 'least favourable' patient profiles. Model parameters were analysed, and the 'most favourable' patient is defined as having characteristics and comorbidities associated with negative coefficients, thus linked to a reduced risk of infection. Similarly, the 'least favourable' patient was defined as having the traits and comorbidities associated with positive coefficients and consequently with an increased risk of BSIs. This approach allowed us to define a range of risk associated with each mechanism, reflecting the variability in propensity to develop BSI across different patient scenarios based on both the MDRO characteristics and the patient profile extremes.

Ethics

The study protocol was written in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The SkyNet Database was approved by the local ethical committee (Comitato Etico Pavia, no. prot. 20,210,068,914).

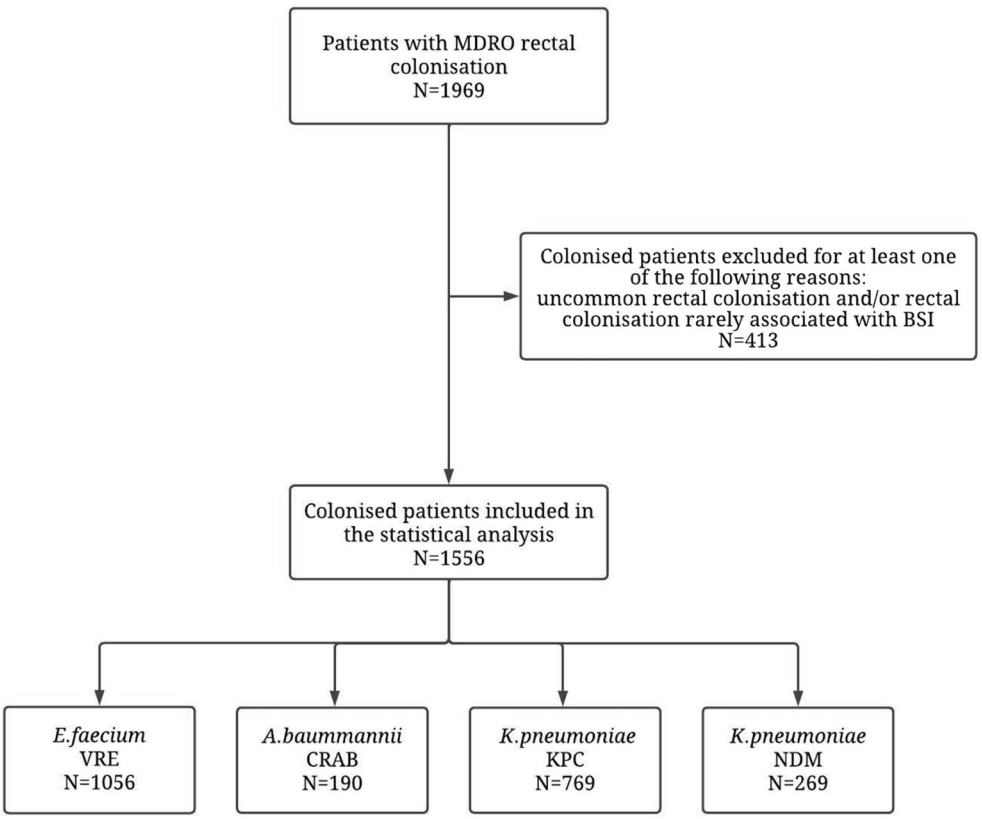

Fig. 1 Flowchart of included and excluded patients. Among 1969 patients with rectal colonisation by multidrug-resistant organisms (MDROs), 413 were excluded owing to uncommon rectal colonisation and/or colonisation types rarely associated with bloodstream infection (BSI). The final statistical analysis included 1556 colonised patients: 1056 with *E. faecium* (VRE), 190 with *A. baumannii* (CRAB), 769 with *K. pneumoniae* (KPC) and 269 with *K. pneumoniae* (NDM)

Table 1 Demographic and clinical characteristics of hospitalisations of patients colonised by *Klebsiella pneumoniae*-producing carbapenemase (KPC) or New Delhi metallo-β-lactamase (NDM), vancomycin-resistant *Enterococcus faecium* (VRE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB)

	KPC	NDM	VRE	CRAB	Overall*
Population (number of hospitalisations)	769	269	1056	190	1960
Age, median (IQR)	64 (55–73)	67 (55–77)	63 (54–73)	63 (53–72)	63 (54–73)
Sex (male)	541 (70%)	179 (66.5%)	626 (59.2%)	148 (77.9%)	1258 (64.2%)
Cardiovascular diseases	293 (38%)	102 (37.9%)	252 (23.8%)	62 (32.6%)	596 (30.4%)
Hypertension	98 (12.7%)	20 (7.4%)	77 (7.3%)	20 (10.5%)	177 (9%)
Diabetes	69 (9%)	16 (5.9%)	66 (6.3%)	10 (5.3%)	140 (7.1%)
Obstructive pulmonary diseases	40 (5.2%)	24 (8.9%)	35 (3.3%)	5 (2.6%)	92 (4.7%)
Chronic kidney diseases	68 (8.8%)	13 (4.8%)	58 (5.5%)	13 (6.8%)	123 (6.3%)
Chronic liver diseases	13 (1.7%)	7 (2.6%)	25 (2.4%)	4 (2.1%)	40 (2%)
Rheumatic diseases	6 (0.8%)	5 (1.9%)	7 (0.7%)	3 (1.6%)	17 (0.9%)
Neoplasia	43 (5.6%)	38 (14.1%)	550 (52.1%)	13 (6.8%)	611 (31.2%)
Solid organ transplant	38 (4.9%)	8 (3%)	45 (4.3%)	6 (3.2%)	78 (4%)
Neutropenia	6 (0.8%)	7 (2.6%)	115 (10.9%)	2 (1%)	125 (6.4%)
Haematological malignancies	12 (1.6%)	16 (5.9%)	304 (28.8%)	4 (2.1%)	324 (16.5%)
Bone marrow transplant	6 (0.8%)	3 (1.1%)	63 (6%)	2 (1%)	70 (3.6%)
Development of BSI	97 (12.6%)	28 (10.4%)	33 (3.1%)	38 (20%)	185 (9.4%)
- Ward -					
Surgical wards	135 (17.55%)	44 (16.36%)	87 (8.24%)	28 (14.74%)	255 (13.01%)
Medical wards	204 (26.54%)	128 (47.58%)	837 (79.26%)	35 (18.42%)	1086 (55.41%)
ICU	430 (55.91%)	97 (36.06%)	132 (12.50%)	127 (66.84%)	619 (31.58%)
Number of patients	684	228	785	184	1556

*Because multiple MDRO colonisations may occur during a single hospitalisation, the overall number of hospitalisations is lower than the sum of those reported for each specific colonisation

RESULTS

A total of 1969 patients were included in the study, accounting for 2541 hospitalisations related to colonisations caused by several MDROs. Among these, 1556 patients (79.0%) and 1960 hospitalisations (77.1%) involved one of the four most frequently represented resistance profiles, namely *Klebsiella pneumoniae* KPC, *Klebsiella pneumoniae* NDM, VRE and CRAB (Fig. 1). The other 413 patients had infrequent colonisations and/or colonisations rarely

Table 2 Associations between demographic, clinical and ward-related factors with BSIs in patients colonised with KPC

KPC	OR	C95	*P*-value
Intercept (baseline: healthy patient in ICU)	0.25	0.18–0.34	< 0.001
Age			
Sex			
Ward 2 (surgical ward ICU)	0.32	0.14–0.63	0.002
Ward 3 (medical ward wrt ICU)	0.32	0.16–0.57	< 0.001
Metabolic syndrome	0.66	0.42–1.02	0.061
Obstructive pulmonary diseases			
Chronic kidney diseases			
Chronic liver diseases	3.29	0.69–11.92	0.090
Rheumatic diseases	0	–	–
Neoplasia			
Solid organ transplant			
Oncohaematology bone marrow transplant	3.22	0.98–9.30	0.037

associated with BSI; details of the different colonisations and BSI are presented in Supplementary Table S1.

Since several patients experienced multiple hospitalisations and acquired different comorbidities over time, we considered hospitalisation as the unit of analysis. Table 1 presents the demographic and clinical characteristics at hospitalisation level rather than at individual patient level.

Moreover, as patients could be colonised with multiple MDROs across different hospitalisations or during the same hospitalisation, the sum of patients across subgroups (KPC, NDM, VRE and CRAB) exceeds the overall number of unique patients included in the study.

The median age of hospitalised patients was 63 years (IQR: 54–73), with a predominance of males (64.2%, 1258/1960). The distribution of hospitalisations across MDROs was as follows: KPC (769), NDM (269), VRE (1056) and CRAB (190).

The overall rate of BSI development was 9.4% (185/1960), with the highest occurrence observed in patients colonised with CRAB (20.0%, 38/190) and KPC (12.6%, 97/769).

Regarding underlying conditions, cardiovascular diseases (30.4%, 596/1960) and neoplasia (31.2%, 611/1960) were the most frequent comorbidities. Other common conditions included hypertension (9%, 177/1960), diabetes (7.1%, 140/1960) and chronic kidney disease (6.3%, 123/1960). Patients colonised with VRE had the highest prevalence of neoplasia (52.1%, 550/1056) and haematological malignancies (28.8%, 304/1056).

Hospitalisation wards varied significantly among the MDRO subgroups. The majority of KPC (55.9%, 430/769) and CRAB (66.8%, 127/190) cases were identified in patients in the ICU, whereas most VRE cases (79.3%, 837/1056) were detected in general medical wards.

Patients in the ICU exhibited the highest rates of BSI for all MDROs, particularly for CRAB (22.83%), NDM (19.59%) and KPC (16.98%). In contrast, lower BSI rates were observed in surgery and clinical wards, with the lowest percentage recorded for NDM in surgery (2.27%) (Supplementary Table S2).

Associations between demographic, clinical and ward-related factors with BSIs in patients

Table 3 Associations between demographic, clinical and ward-related factors with BSIs in patients colonised with NDM

NDM	OR	C95	*P*-value
Baseline (healthy patient in ICU)	0.13	0.05–0.32	< 0.001
Age			
Sex	2.43	0.94–7.60	0.089
Ward 2 (surgical ward wrt ICU)	0.09	0.01–0.47	0.022
Ward 3 (medical ward wrt ICU)	0.26	0.16–0.57	0.002
Metabolic syndrome			
Obstructive pulmonary diseases			
Chronic kidney diseases			
Chronic liver diseases			
Rheumatic diseases			
Neoplasia			
Solid organ transplant Oncohaematology bone marrow transplant	0	–	–

Table 4 Associations between demographic, clinical and ward-related factors with BSIs in patients colonised with VRE

VRE	OR	C95	*P*-value
Baseline (healthy patient in ICU)	0.05	0.02–0.11	< 0.001
Age			
Sex	1.91	0.89–4.44	0.111
Ward 2 (surgical ward wrt ICU)	0.50	0.11–1.73	0.305
Ward 3 (medical ward wrt ICU)	0.16	0.05–0.46	< 0.001
Metabolic syndrome			
Obstructive pulmonary diseases			
Chronic kidney diseases	0	–	–
Chronic liver disease			
Rheumatic diseases			
Neoplasia			
Solid organ transplant Oncohaematology bone marrow transplant	4.07	1.61–11.64	0.004

Table 5 Associations between demographic, clinical and ward-related factors with BSIs in patients colonised with CRAB

CRAB	OR	C95	*P*-value
Baseline (healthy patient in ICU)	0.25	0.17—0.36	< 0.001
Age			
Sex			
Ward 2 (surgical ward wrt ICU)			
Ward 3 (medical ward wrt ICU)			
Metabolic syndrome			
Obstructive pulmonary diseases			
Chronic kidney diseases	0	–	–
Chronic liver diseases			
Rheumatic diseases			
Neoplasia			
Solid organ transplant	11.83	1.47–243.13	0.034
Oncohaematology bone marrow transplant			

colonised with MDROs are presented in Table 2, 3, 4 and 5.

With regard to KPC, patients hospitalised in surgical ward (OR = 0.25, $p = 0.002$) and in clinic (OR = 0.32, $p < 0.001$) had a significantly lower likelihood of developing BSI with respect to ICU.

Oncohaematology diseases and BMT were significantly associated with an increased risk of BSI (OR = 3.22, $p = 0.037$). Other clinical conditions, including rheumatic diseases, chronic kidney disease and chronic liver disease, did not show significant associations (Table 2).

Similarly, for NDM, hospitalisations in surgical (OR = 0.09, $p = 0.022$) and in medical wards (OR = 0.26, $p = 0.002$) were significantly associated with a reduced likelihood of BSI with respect to the ICU (Table 3).

Regarding VRE, hospitalisation in medical wards was significantly associated with a lower likelihood of BSI (OR = 0.16, $p < 0.001$). Conversely, oncohaematology and BMT were associated with a significantly increased risk of BSI (OR = 4.07, $p = 0.004$). Chronic kidney disease and chronic liver disease did not show significant associations (Table 4).

For CRAB, the only comorbidity significantly associated with an increased risk of BSI was SOT (OR = 11.83, $p = 0.034$). No significant associations were found for ward of hospitalisation, metabolic syndrome or chronic kidney and liver diseases (Table 5).

Analysis of Prototypic Patients

Patients' profiles with the highest and lowest likelihood of developing BSI are shown in Fig. 2 and presented in Supplementary Table S3.

Among patients colonised with KPC, the most favourable profile corresponded to individuals hospitalised in clinical wards with metabolic syndrome, presenting the lowest probability of developing BSI [0.05 (0.03, 0.09)]. Conversely, the least favourable profile was observed in patients admitted to the ICU with chronic liver disease and oncohaematologic disease or having undergone a BMT, who exhibited the highest risk [0.72 (0.30, 0.94)].

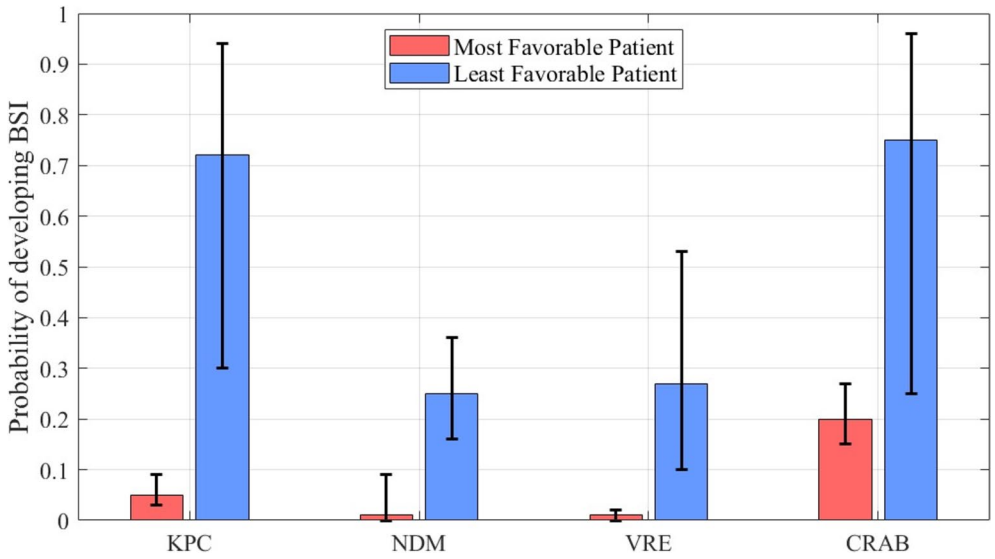

Fig. 2 Analysis of prototypic patients. Profiles of MDRO-colonised patients with the highest and lowest likelihood of developing BSI starting from the relative colonisation were identified on the basis of the estimated logistic regression models. Predicted probability of developing bloodstream infection (BSI) for the most and least favourable patient profiles colonised by KPC, NDM, VRE and CRAB. Red bars represent the most favourable profiles – i.e. those with the lowest estimated probability of BSI – while blue bars represent the least favourable profiles – i.e. those with the highest estimated probability. Error bars denote 95% confidence intervals. Detailed patient characteristics for each profile are presented in Table S3.

Regarding patients colonised with NDM, the lowest probability of BSI was identified in female patients undergoing surgery [0.01 (0.00, 0.09)]. In contrast, the highest risk was associated with male patients in the ICU, who had a markedly increased likelihood of BSI [0.25 (0.16, 0.36)].

For VRE-colonised patients, hospitalisation in medical wards was associated with the lowest risk of BSI, particularly in female patients, who had a predicted probability of 0.01 [0.00, 0.02]. However, the highest probability of BSI was observed in male patients in the ICU with oncohaematologic disease or BMT, with an estimated risk of 0.27 [0.10, 0.53].

Finally, for patients colonised with CRAB, the lowest risk of BSI was identified in otherwise healthy individuals [0.20 (0.15, 0.27)]. In contrast, SOT was associated with the highest probability of BSI [0.75 (0.25, 0.96)], highlighting the significant impact of this comorbidity on infection risk.

DISCUSSION

In this study, we identified KPC, NDM, VRE and CRAB as the most frequently observed MDROs responsible for colonisation and subsequent BSI. The overall rate of BSI was 9.4%, with CRAB and KPC showing the highest rates (20.0% and 12.6%, respectively). Regarding CRAB, our findings align with previous studies reporting an increased risk of BSI in patients in the ICU colonised with this particularly aggressive MDRO [7]. Similarly, other studies have highlighted the propensity of carbapenemase-producing *Klebsiella pneumoniae* to cause infections from rectal colonisation, although they did not differentiate between specific carbapenemase variants [4, 8]. Interestingly, Falcone et al. identified a higher rate of BSI in patients colonised with *Klebsiella pneumoniae* NDM compared with KPC, which differs from our findings [9]. However, at the time of their study, a significant outbreak of a particularly virulent *Klebsiella pneumoniae* NDM strain was ongoing, which may explain their

results [10]. The infection rates observed in our study align with those reported in a recent study by Karakosta et al., which documented BSI rates of 3.5% among VRE carriers, 15.6% among CRE carriers and 19.6% among CRAB carriers[11].

Our study also identified several key risk factors associated with the development of BSI, including the ward of hospitalisation, underlying comorbidities and the specific MDRO involved. Notably, patients with oncohaematologic diseases or those undergoing BMT had an increased risk of developing BSI, particularly in VRE- and patients colonised with KPC. This is consistent with existing literature indicating that immunocompromised patients, particularly those undergoing intensive treatments, are highly susceptible to MDRO infections [12–14]. Similarly, patients hospitalised in the ICU had a higher overall risk of developing BSI, particularly when colonised with KPC and NDM. This aligns with previous reports showing that patients in the ICU face heightened risk owing to their critical conditions and frequent exposure to invasive medical interventions, such as central venous catheters and mechanical ventilation [15]. The intensive nature of the ICU increases the likelihood of pathogen translocation, leading to BSIs [16].

However, we did not observe a statistically significant difference between ICUs and other inpatient areas in terms of BSI risk for patients colonised with CRAB. This may be attributable to the fact that most CRAB colonisation cases were in patients in the ICU, with fewer cases in general medical or surgical wards, limiting the statistical power to detect meaningful differences.

In contrast, we observed that VRE was predominantly found in medical wards, which are often dedicated to older or more frail patients. Despite a high colonisation burden, these patients exhibited a lower BSI rate. This suggests that while medical wards may have a greater prevalence of colonisation, the lower intensity of invasive procedures in these settings may reduce BSI risk [17].

Comorbidities played a significant role in determining the risk of BSI. Specifically, the presence of neoplasia and haematologic malignancies was strongly associated with an increased risk of BSI in patients colonised with VRE and KPC. This aligns with literature indicating that immunocompromised patients, particularly those undergoing chemotherapy, are at significantly higher risk owing to their compromised immune defences and alterations of intestinal mucosa, facilitating translocation of MDROs [13].

The risk of BSI was also influenced by the specific MDRO involved. Patients colonised with CRAB in ICU settings, particularly those with oncohaematologic diseases, had the highest probability of progressing to BSI. Similarly, patients with KPC colonisation in ICU settings and haematologic malignancies demonstrated a high probability of BSI. These findings highlight the need for rigorous monitoring and tailored preventive measures for high-risk patients, particularly in ICU settings.

Conversely, *Klebsiella pneumoniae* NDM-colonised patients exhibited a generally lower risk of developing BSI (1%), although patients in the ICU still showed a 25% probability of progression, warranting continued attention for this vulnerable group [10]. For VRE colonisation, as previously reported [18], the overall risk of transition to BSI was low in the general population but increased significantly in oncohaematologic patients or those undergoing BMT (27%). Given the heightened risk of both BSI and related mortality in this subgroup, stringent surveillance protocols and infection control measures are imperative [19].

These findings suggest a potential stratification of MDROs on the basis of their likelihood of causing BSI, with CRAB and KPC posing the highest risk, particularly in patients in the ICU, followed by VRE in immunocompromised hosts and a lower risk associated with NDM.

While such a ranking may be useful for risk assessment and infection control strategies, it is essential to interpret these findings with caution, as multiple patient-specific and environmental factors influence BSI development.

This study has some limitations. First, its retrospective nature introduces the potential for selection bias. In particular, screening protocols for rectal colonisation varied depending on hospital ward and patient risk profile. While screening was routinely implemented in ICUs and for haematologic patients, in other settings it was

reserved for high-risk individuals, such as those transferred from other institutions. This heterogeneity may have led to an underestimation of colonisation prevalence in certain populations and affected the comparability of data across wards.

Moreover, information on patient comorbidities was extracted from hospital discharge records using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, which were subsequently aggregated into clinical macro-groups. Although this allowed for a standardised assessment, the level of detail may not fully capture the clinical complexity of individual patients. In addition, owing to limitations of the dataset, we were unable to collect information on antimicrobial treatments administered prior to or during hospitalisation. Another limitation concerns the microbiological methodology. While colonisation and infection were defined on the basis of the identification of the same MDRO species and resistance mechanism from rectal swabs and blood cultures, molecular typing was not performed. It is therefore possible that some infections were caused by different strains of the same species sharing identical resistance phenotypes. However, given the consistency in species and resistance patterns, it is likely that the same strain was involved, although this cannot be confirmed without molecular sequencing. Lastly, while our analysis explored multiple variables and incorporated prototypic patient profiles, unmeasured confounding factors may still influence the risk of BSI. For example, details regarding the timing of invasive procedures, the use of central venous catheters and infection prevention measures at the patient level were not available, all of which could significantly affect infection risk.

Despite these limitations, the study provides meaningful insights into the complex relationship between colonisation and infection in patients with MDROs, highlighting the importance of tailored preventive strategies and targeted surveillance in high-risk populations.

CONCLUSIONS

Our study highlights the critical role of MDRO colonisation in the development of BSIs, especially in high-risk populations such as patients in the ICU and those with oncohaematologic diseases or undergoing BMT and SOT. Consequently, tailoring empirical antibiotic therapy on the basis of MDRO colonisation status and patient clinical profiles is crucial to balancing effective treatment with the prevention of excessive broad-spectrum antibiotic use, which could contribute to further resistance and poor outcomes [20, 21]. Given our observed rates of BSI following specific MDROs colonisations, empirical coverage for CRAB and KPC may be considered in patients in the ICU, with these pathogens' colonisation. Conversely, VRE may be considered primarily in those with oncohaematologic diseases or undergoing BMT. However, these considerations should be interpreted with caution, and further studies are needed to validate risk-based approaches to empirically treat patients colonised with MDRO.

Finally, our findings suggest that enhanced infection control measures may be particularly necessary in ICUs to prevent the progression of MDRO colonisation to BSI.

Author Contributions. Marta Colaneri: conceptualisation, formal analysis, data curation, methodology, validation, visualisation, writing—original draft; Paola Giordani: conceptualisation, data curation, methodology, validation, writing—original draft; Simone Milanesi: conceptualisation, data curation, formal analysis, writing, methodology, visualisation; Elena M. Tosca: conceptualisation, formal analysis, methodology; Sonia Lerta, Aurelia Sangani, Vincenzo A. Villano and Marco Rettani: data curation; Alba Muzzi, Marta Corbella, Patrizia Cambieri and Andrea Gori: supervision, review; Raffaele Bruno: conceptualisation, supervision, review; Giuseppe De Nicolao: conceptualisation, formal analysis, data curation, methodology, validation, visualisation. All authors have read and agreed to the published version of the manuscript.

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Data Availability. The data presented in this study are available on request from the corresponding author.

Declarations

Conflict of Interest. Marta Colaneri, Paola Giordani, Simone Milanesi, Sonia Lerta, Elena M. Tosca, Aurelia Sangani, Vincenzo A. Villano, Marco Rettani, Alba Muzzi, Marta Corbella, Patrizia Cambieri, Andrea Gori, Giuseppe De Nicolao and Raffaele Bruno declare no conflicts of interest.

Ethical Approval. This retrospective study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments.

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