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Factors associated with colonization by carbapenem-resistant enterobacteria in oncological patients: a case-control study

Fatores associados à colonização por enterobactérias resistentes a carbapenêmicos em pacientes oncológicos: um estudo caso-controle

Factores asociados a la colonización por enterobacterias resistentes a carbapenémicos en pacientes con cáncer: un estudio caso-control

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ABSTRACT

Introduction: Colonization and infections caused by Carbapenemase Producing Enterobacteria (CPE) are a global problem, being associated with an increase in hospitalization time, costs for health services, and morbidity and mortality rates. Oncologic patients represent a group of special interest and there are few studies involving CPE colonization among these patients. **Aim:** to investigate factors associated with colonization in cancer patients. **Outlining:** Case-control study developed in a tertiary reference hospital in cancer treatment in Porto Alegre, Brazil, from January to December 2017. The population consisted of patients diagnosed with cancer in clinical or surgical hospitalization. **Results:** The univariate analysis showed that variables associated with colonization by CPE were age, male sex, tumors with bone type of surgical hospitalization, number of intra-hospital transfers since hospitalization, hospitalization time >30 days, ICU hospitalization in the last 30 days, ICU time more than 15 days, surgical procedure in the last 30 days, use of antibiotics in the last 30 days, presence of tumor wound, and KPC infection. After multivariate analysis, male sex, external hospital as origin, hospital stay longer than 30 days, antibiotic use in the last 30 days, and presence of tumor wound, remained associated with EPC colonization. Use of aminoglycosides, and linezolide were associated with CPE colonization. **Implications:** We identified variables associated with CPE colonization in oncologic patients. Our results may indicate actions to prevent CPE colonization and consequent development of infections.

DESCRIPTORS

Drug Resistance, Multiple; Infection Control; Risk Factors; Carbapenem-Resistant Enterobacteriaceae.

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INTRODUCTION

The emergence and spread of Carbapenemase-Producing-Carbapenemase (CRE) - resistant Enterobacteriaceae is a major public health problem, emerging as a global threat in the last decade.[1] These micorganisms are associated with an increase in hospitalization length of stay, costs for health services, and morbidity and mortality rates. The occurrence of carbapenem-resistant Enterobacterales (CRE), particularly those carbapenemase-producing ones (CPE), has restricted therapeutic options. Furthermore, mortality rates associated with CRE infection range from 24% to as high as 70%.[2]

The most important carbapenemases produced by Enterobacterales are class A enzymes, such as *K. pneumoniae* carbapenemase (KPC); class B metallo-beta-lactamases (MBL), including New Delhi metallo-ß-lactamase (NDM) and Oxacilinase Class D (OXA)-48 and variants thereof.

Organ transplants, intensive care unit (ICU) hospitalizations, complex surgical procedures, prolonged hospitalizations, and oncological and onco-hematological diseases are also impacted with infections due to CRE and increasing in antimicrobial resistance. For this reason, oncologic patients may represent a group of special interest and there are few studies involving CRE colonization among them.[1] Besides, oncological and onco-hematological diseases are also associated with microbial resistance. Moreover, an early and rapid identification of colonized hospitalized patients is mandatory to avoid the spread of these highly resistant pathogens.[3]

Research and knowledge about multidrug-resistant bacteria are relevant in order to limit their dissemination, encouraging the reduction of morbidity and mortality rates, accompanied by microbiological surveillance. Outbreaks in the hospital environment has been highlighted as a challenge to be considered, since it has become a difficult problem to solve. It is also necessary to consider the increasing number of patients with different conditions, as well as the frequency of immunosuppression conditions.

Considering that there are few studies involving CRE colonization among these oncological patients, the aim of this study was to investigate factors associated with CRE colonization in oncologic patients.

METHOD

A retrospective observational case-control study was conducted among patients aged ≥ 18 years from January 2017 to December 2017. This study was carried out at Santa Rita Hospital, a tertiary-care hospital and a national reference in oncology, which belongs to the Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) Hospital Complex. Santa Rita Hospital has approximately 192 clinical and surgical beds, ten ICU beds and seven operating rooms.

According to the institution's protocol, all hospitalized patients are submitted to surveillance for CRE colonization through rectal swabs obtained once a week from all patients, until discharge. In patients who have received some type of care (hospitalization or long-term care facility) in external or internal health services in the last 30 days, hemodialysis, endoscopy, chemotherapy, radiotherapy) and after hospitalization in ICU for more than 24 hours, rectal swabs were obtained at hospitalization in our institution.

Screening for case and control selection was based on the annual report provided by the institution's Infection Control Service (2,500 swabs with negative results and 1,500 positive swabs). In accordance with the institution's protocol for detecting CRE, a rectal swab is obtained weekly from each patient. In this way, the research is repeated until obtaining a positive culture.

A case is defined as a patient who presents for the first time a CRE in a surveillance culture. For the patient to be considered colonized within the institution's protocols, he or she must be hospitalized

for a period longer than 48 hours; in such situation, colonization is considered previous or external, not being considered a case in the study. Also, through a detailed review (information was taken from the SCI database and later confirmed in a medical record), we excluded any possibility that the patient, in the previous six months, had been colonized or infected with enterobacteria resistant to carbapenems. Patients with duplicate results were included only once in the study. For each case, two controls were included. Inclusion criteria for cases: patient admitted to any hospital ward during the study period, colonization by CRE (a positive surveillance culture) at least 48 hours of admission, without CRE isolation from any biological specimen within 6 previous months. Patients with incomplete medical records were excluded. Patients with negative CRE rectal swabs, admitted to the same ward and at the same time of cases were included as controls. We estimated a sample size of about 130 patients with two corresponding controls for each patient (approximately 260 controls).

The specimens were processed based on previously described protocol,[4] briefly described here: Swabs were planted on a KPC chromogenic medium (CHROMagar KPC Plastlabor) for detection of carbapenem resistance. After 24 hours of incubation, colonies with morphology compatible with Enterobacterales were identified at species level by MALDI-TOF. Carbapenemase production was confirmed by the modified CarbaNP test.[5] All isolates with a positive result in CarbaNP test were subjected to a previously described single multiplex real-time PCR assay to detect six carbapenemases genes (bla_{NDM-1}, bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{GES} and bla_{OXA48}).[6] Briefly, after bacterial DNA extraction, amplification procedure using specific primers for each carbapenemase target was performed. Each one of the six carbapenemase genes tested presented a different melting curve after PCR amplification that allowed us to identify the gene present.

The variables potentially associated with CRE colonization included: age, sex, diagnosis, topography of oncological disease, clinical or surgical hospitalization (considered at admission), number of intra-hospital transfers, hospitalization in the last 3 months, hospital length of stay, hospitalization in the intensive care unit in the last 30 days for more than 24 hours, length of ICU stay, previous surgical procedure during hospitalization in the last 30 days, antimicrobial exposure in the last 30 days (only antimicrobials used for at least 48 hours) presence of wounds during hospitalization, radiotherapy in the last 30 days, chemotherapy in the last 30 days, infections. The searches were performed in medical records. Chemotherapy and/or radiotherapy were defined as the use of cytotoxic antineoplastic drugs or ionizing radiation.[7]

For the descriptive analysis, the quantitative variables were presented by mean and standard deviation or median and interquartile range. Categorical variables were described by absolute and relative frequencies. Univariate and multivariate analyzes were performed. In the univariate analysis, t-student tests were applied for independent samples (quantitative variables of symmetrical distribution), Mann-Whitney (asymmetric quantitative variables) or chi-square supplemented by the analysis of the adjusted residuals (categorical variables). For multivariate analysis, in the control of potential confounding factors, a logistic regression model with backward extraction method, and odds ratio and confidence interval to measure the effect of each factor were used for the variables with a value of $p < 0.20$ in the univariate analysis. A value of $p < 0.05$ was considered to indicate statistical significance. All data were analyzed with SPSS version 21.0 (IBM-SPSS Inc, Armonk, NY). The research was approved by the Research Ethics Committee of the Santa Casa de Misericórdia Hospital of Porto Alegre, under protocol number 2.157.743.

RESULTS

Of the 139 CRE isolates, the most commonly identified were *Klebsiella pneumoniae* (n=93), followed by *Enterobacter* ssp (n=25), *Citrobacter freundii* (n=8), *Escherichia coli* (n=6), *Klebsiella oxytoca* (n=3), *Aeromonas hydrophila* (n=2) *Raoutella ornithinolytica* (n=1), and *Serratia spp* (n=1). Carbapenemase was detected in all cases, including 103 (74.1%) bla_{KPC} , 20 (14.3%) bla_{NDM-1} and 6 (11.5%) cases of bla_{KPC} and bla_{NDM} coproduction (Table 1).

Table 1 - Distribution of microorganisms and carbapenemase-producing genes among 139 carbapenemase-resistant enterobacteria obtained from rectal cultures from patients at Hospital Santa Rita, January-December 2017.

Microorganism	*bla*KPC (%)	*bla*NDM-1(%)	*bla*KPC + *bla*NDM-1 (%)	Total (%)
Klebsiella pneumoniae	78 (75.7)	3 (15.0)	12 (75.0)	93 (66.9)
Enterobacter spp	13 (12.6)	11 (55.0)	1 (6.3)	25 (18.0)
Other	12 (11.7)	6 (30.0)	3 (18.7)	21 (15.1)
Total	103 (100)	20 (100)	16 (100)	139 (100)

Demographic and clinical characteristics of cases and controls are presented in table 2. The univariate analysis showed that the variables significantly associated with differences in cases and controls were age (p=0.036), male sex (p=0.007), topography of the tumor (p=0.027), surgical hospitalization (p=0.012), number of intra-hospital transfers since hospitalization (p≤0.001), hospitalization time >30 days (p≤0.001), ICU hospitalization in the last 30 days (p≤0.001), ICU time of more than 15 days (p≤0.001), surgical procedure in the last 30 days (p=0.024), use of antimicrobial in the last 30 days (p≤0.001), and presence of tumor wound (p=0.015).

Table 2 - Univariate analysis and multivariate Logistic Regression Analysis of factors associated with carbapenem-resistant enterobacteria from patients at Santa Rita Hospital, January-December 2017.

	Univariate analysis			Multivariate Logistic Regression Analysis	
Variables	**Cases (n=139)**	**Controls (n=278)**	**p**	**OR (IC 95%)**	**p**
Age (years) - mean ± DP	60.8 ± 17.3	64.4 ± 14.0	0.036		
Sex - n (%)			0.007		
Male	89 (64.0)	138 (49.6)		2.18 (1.35-3.53)	0.001
Diagnosis - n (%)			0.166		
Solid tumor	112 (80.6)	240 (86.3)			
Hematologic	27 (19.4)	38 (13.7)			
Topography of the tumor - n (%)			0.027		
Hematological	27 (19.4)	39 (14.0)			
Respiratory tract	26 (18.7)	36 (12.9)			
Neurological	3 (2.2)	2 (0.7)			
Urinary tract	3 (2.2)	13 (4.7)			
Reproductive tract	23 (16.5)	58 (20.9)			
Integumentary	3 (2.2)	12 (4.3)			
Digestive tract	43 (30.9)	111 (39.9)			
Endocrine	3 (2.2)	2 (0.7)			
Bone	8 (5.8)*	5 (1.8)			
Type of hospitalization - n (%)			0.012		
Surgical	60 (43.2)	84 (30.2)		2.23 (1.08-4.59)	0.030
Clinical	79 (56.8)	194 (69.8)			
Number of swab collections - median (P25-P75)	3 (2 – 5)	3 (1 – 4)	0.200		

Number of intra-hospital transfer - median (P25-P75)	2 (1 - 3)	1 (1 - 2)	<0.001		
Hospitalization in the last 3 months - n (%)	79 (56.8)	178 (64.0)	0.188		
Hospitalization time - n (%)			<0.001		
<30 days	51 (36.7)	190 (68.3)			
≥30 days	88 (63.3)	88 (31.7)		3.25 (2.01-5.25)	<0.001
ICU in the last 30 days - n (%)	59 (42.4)	49 (17.6)	<0.001	2.33 (1.31-4.14)	0.004
ICU time (days) - n (%)			<0.001		
<5 days	12 (20.7)	25 (51.0)*			
5-15 days	31 (53.4)	22 (44.9)			
>15 days	15 (25.9)*	2 (4.1)			
Surgical procedure in the last 30 days - n (%)	62 (44.6)	91 (32.7)	0.024		
Use of antimicrobial in the last 30 days - n (%)	111 (79.9)	153 (55.0)	<0.001	2.48 (1.41-4.35)	0.002
Wounds - n (%)			0.015		
No wounds	76 (54.7)	191 (68.7)*		1.00	
Operative	46 (33.1)	71 (25.5)		0.83 (0.38-1.79)	0.632
Tumor	13 (9.4)*	10 (3.6)		4.11 (1.50-11.2)	0.006
Wound Pressure	4 (2.9)	6 (2.2)		1.39 (0.34-5.69)	0.645
Radiotherapy - n (%)	13 (9.4)	33 (11.9)	0.543		
Chemotherapy - n (%)	41 (29.5)	86 (30.9)	0.851		

*Variable with significance in the category

Considering the use of antimicrobials in the 30 previous days, piperacillin-tazobactam was the most used, follow by carbapenems and cephalosporins (Table 3). The use of the following antimicrobial agents was significantly associated with CRE: piperacillin/tazobactam (p=0.003), carbapenems (p=0.039), linezolid (p=0.019), and aminoglycosides (p<0.001).

Table 3 - Case-control comparison of antibiotic use by class from patients at Santa Rita Hospital, January-December 2017.

Variables	Cases (n=139)	Controls (n=278)	p
Piperacillin-tazobactam	70 (50.4)	96 (34.5)	0.003*
Fluoroquinolones	14 (10.1)	22 (7.9)	0.579
Carbapenem	32 (23.0)	40 (14.4)	0.039*
Vancomycin	13 (9.4)	23 (8.3)	0.853
Cephalosporin	23 (16.5)	40 (14.4)	0.663
Polymyxin B	10 (7.2)	9 (3.2)	0.115
Ampicillin + Sulbactam	11 (7.9)	30 (10.8)	0.450
Linezolid	6 (4.3)	2 (0.7)	0.019*
Daptomycin	2 (1.4)	1 (0.4)	0.259
Aminoglycosides	20 (14.4)	4 (1.4)	<0.001*
Clindamycin	7 (5.0)	5 (1.8)	0.115

*Statistically significant for CRE colonization (p<0.05).

In 25 (18%) of the cases a CRE isolate was obtained from a clinical specimen sometime after colonization. In a subsequent multivariate analysis (Table 2), male sex (OR = 2.18, 95% CI: 1.35-3.534.38; p=0.001), surgical hospitalization (OR = 2,23, 95% CI: 1.08-4.59; p=0,030), hospital stay longer than 30 days (OR = 3,25, 95% CI: 2,01-5.25, p = <0.001), ICU in the last 3 months (OR=2,33,95% CI: 1,31-4,14); p=0.004, antibiotic use in the last 30 days (OR = 2,48, 95% CI: 1,41-4,35; p = 0.002), and presence of tumor wound (OR = 4,11, 95% CI:1.50-11.2, p=0.006), remained as factors significantly associated with CRE colonization. The following antibiotics were found to be statistically significant after adjustment for each

type of antibiotic: aminoglycosides (OR = 7.95, 95% CI: 2.44-25.9; p=0.001), and linezolid (OR = 3 .95, 95% CI: 1.12-13.9; p=0.032).

DISCUSSION

In this case-control study we identified an association of CRE colonization with variables such as male sex, type of hospitalization, time of hospitalization, hospitalization in ICU, previous use of antimicrobial agents, and presence of a tumor wound. CRE are increasingly prevalent in health institutions and their worldwide dissemination contributes to morbidity and mortality, leading to the need for active surveillance to identify and investigate associated factors.[8]

Although there are studies on the prevalence and dissemination of ERC, there are relatively few studies that specifically address factors associated with colonization and infection by these microorganisms, especially among cancer patients.

We observed an association between male sex and CRE colonization. A recent study showed an association between male sex and the development of infection caused by carbapenemase-producing enterobacteria, when this group was compared to the group of patients infected with enterobacteria with non-susceptible carbapenems by mechanisms other than carbapenemase production. Such association had previously been described for the acquisition of other microorganisms.[9]

Our study demonstrates the marked capacity of dissemination of carbapenemases among different bacterial species, which is consistent with previous studies.[10] Although most cases occurred due to colonization by KPC-producing K. pneumoniae, a wide variety of Enterobacterales was described. It is interesting to note that blaKPC production was mostly related to K. pneumoniae (in only three cases the enzyme was not detected in carbapenem-resistant isolates of this species), whereas the occurrence of NDM-producing isolates was more related to Enterobacter spp. This fact corroborates reports of worrisome dissemination at both national and international levels.[11]

The univariate analysis indicated different factors potentially associated with CRE colonization and allowed us to deeply investigate the influence of such factors. Surgery has been reported as a risk factor for colonization by CRE.[12-13]

The treatment of cancer patients is challenging due to the exposure of intensive chemotherapy protocols, the use of monoclonal antibodies or other biological agents, the increasing age of patients with cancer disease and the frequent presence of multiple comorbidities.[14] The patients with hematologic malignancies and recipients of hematopoietic stem cell transplants (HSCT) are at high risk of developing invasive infections due to enteric bacteria due to chemotherapy-induced neutropenia and gastrointestinal mucositis.[1]

Thus, our study strengthens this association with surgical procedures, and patients undergoing surgery are usually hospitalized in the long term, which could increase the risk of exposure. In the multivariate analysis, we identified length of hospital stay as a factor associated with colonization due to CRE, as described in other studies.[12-13] Since our hospital is a national tertiary reference center for oncological care, most patient on oncological disease treatment undergo prolonged medical treatment and are exposed to multiple and prolonged hospitalizations, and to extensive use of broad-spectrum antimicrobials.[15] This may explain the high CRE prevalence among these patients. Hospitalization in ICU is also typically associated with resistance development, what was confirmed in our study.

Previous antibiotic use was significantly associated with CRE colonization; previous studies have shown that recent antimicrobial use may be a risk factor for colonization due to CRE.[16-19] The antimicrobials that stood out were piperacillin-tazobactam, carbapenems, linezolid and aminoglycosides. Treatment with carbapenems prior

to colonization correlates with previous reports.[20] Carbapenem use is a well-defined factor associated with CRE, although this association was not present in some studies.[18,21] These discrepancies among the studies merit careful analysis but may be related to different definitions of antimicrobial exposure and the possibility of uncontrolled confounders in retrospective studies.[22] Piperacillin-tazobactam is widely used in our institution, what represents a cause for concern, since it has been associated with colonization by CRE. To the best of our knowledge, the association of colonization (or infection) by CRE and use of aminoglycosides or linezolid has not been previously described. Linezolid is selectively used in our hospital and its role as suppressor of gram-positive microbiota seems to confer advantages for survival of enterobacteria in the intestinal environment. Interestingly, the use of linezolid as a selective agent enhances the in vitro detection of CRE when applied to surveillance cultures.[23]

Wounds influence the outcome of clinical treatment. Oncological lesions merit a specific approach to each patient.[24] This is the first study that identified oncological wounds as a factor associated with colonization with CRE, raising a specific discussion not yet explored in previous studies.

Measures to address patient-to-patient transmission include: hand hygiene, contact isolation precautions, environmental cleanliness, decolonization protocols, and surveillance programs to identify the asymptomatic carrier. In contrast, tackling the resistance effort requires the application of antimicrobial stewardship policies to avoid the necessary use of broad-spectrum agents, especially carbapenems.[25] In Brazil, ANVISA[4] defines a series of specific measures, such as: importance of hand hygiene, use of personal protective equipment (PPE), isolation of colonized and infected patients, epidemiological surveillance system, Active Hospital Infection (CCIH), rational use of antimicrobials, among others. In this way, the early identification of asymptomatic carriers by active surveillance cultures is an ideal strategic approach to track the carriage of these bacteria, to explain transmission and control outbreaks.[25]

In our institution, the use of surveillance cultures is a well established practice. This approachhas become an essential tool in infection control programs, not only during outbreaks, but also as a routine measure in ERC-endemic settings. Screening patients to identify asymptomatic colonization and instituting preventive contact isolation measures such as patient-to-patient screening and colonization pressure improve patient outcomes.[25]

Our study has limitations because the data are collected in a single center and because it was a retrospective analysis, so we may not be able to control all possible confounding factors. Many studies on the subject have been identified in the literature, but few focused exclusively on CRE colonization, instead of on infection. External validation of oncological patients hospitalized in large tertiary hospitals with high levels of CRE may be useful to evaluate the reproducibility of our results. It is important to highlight that the microorganisms in some of the cases may have acquired the gene responsible for the resistance during the hospitalization period. Unfortunately, our study did not analyze the clonality of the isolates, which could have provided the conditions to identify this subpopulation.

CONCLUSION

We identified factors associated with transmission (surgical hospitalization, hospital stay, including ICU, and presence of a tumor wound). We emphasize the association with previous antimicrobial use., which may serve as a basis for the adoption of strategies for better use of antimicrobials. Our results emphasize the need of a strict control at oncology unit in order to avoid the burden of CRE colonization.

RESUMO

Introdução: A colonização e as infecções causadas por Enterobactérias Produtoras de Carbapenemases são um problema global, estando associadas ao aumento do tempo de internação, aos custos para os serviços de saúde, e às taxas de morbimortalidade. Os pacientes oncológicos representam um grupo de especial interesse e há poucos estudos envolvendo a colonização por EPC entres esses pacientes. **Objetivo:** Investigar fatores associados à colonização em pacientes com câncer. **Delineamento:** Estudo caso-controle desenvolvido em um hospital terciário de referência no tratamento oncológico de Porto Alegre, Brasil, no período de janeiro a dezembro de 2017. A população foi composta por pacientes diagnosticados com câncer em internação clínica ou cirúrgica. **Resultados:** A análise univariada mostrou que as variáveis associadas à colonização por EPC foram idade, sexo masculino, tumores do tipo ósseo de internação cirúrgica, número de transferências intra-hospitalares desde a internação, tempo de internação superior a 30 dias, internação em UTI nos últimos 30 dias, tempo de internação em UTI superior a 15 dias, procedimento cirúrgico nos últimos 30 dias, uso de antibióticos nos últimos 30 dias, presença de ferida tumoral, e infecção por KPC. Depois da análise multivariada, o sexo masculino, externo ao hospital como origem, estadia no hospital superior a 30 dias, uso de antibióticos nos últimos 30 dias, e presença de ferida tumoral permaneceram associados à colonização por EPC. O uso de aminoglicosídeos e linezolida foram associados à colonização de EPC. **Implicações:** Identificamos variáveis associadas à colonização por EPC em pacientes oncológicos. Nossos resultados podem indicar ações para prevenir a colonização do CPE e consequente desenvolvimento de infecções.

DESCRITORES

Resistência a Múltiplos Medicamentos; Controle de Infecções; Fatores de Risco; Enterobacteriáceas Resistentes a Carbapenêmicos.

RESUMEN

Introducción: La colonización y las infecciones causadas por enterobacterias productoras de carbapenemasas son un problema global, asociado con mayor duración de la estancia hospitalaria, costos de los servicios de salud y tasas de morbilidad y mortalidad. Los pacientes con cáncer representan un grupo de especial interés y existen pocos estudios que involucren la colonización de EPC entre estos pacientes. **Objetivo:** Investigar factores asociados a la colonización en pacientes con cáncer. **Delineación:** Estudio de casos y controles desarrollado en un hospital terciario de referencia en el tratamiento del cáncer en Porto Alegre, Brasil, de enero a diciembre de 2017. La población estuvo constituida por pacientes diagnosticados con cáncer sometidos a hospitalización clínica o quirúrgica. **Resultados:** El análisis univariado mostró que las variables asociadas a la colonización del EPC fueron edad, sexo masculino, tumores de tipo óseo provenientes del ingreso quirúrgico, número de traslados intrahospitalarios desde el ingreso, tiempo de estancia mayor a 30 días, ingreso a UCI en los últimos 30 días, estancia en UCI mayor a 15 días, procedimiento quirúrgico en los últimos 30 días, uso de antibióticos en los últimos 30 días, presencia de herida tumoral e infección por KPC. Después del análisis multivariado, el sexo masculino, el origen externo al hospital, la estancia hospitalaria mayor a 30 días, el uso de antibióticos en los últimos 30 días y la presencia de una herida tumoral continuaron asociados con la colonización por EPC. El uso de aminoglucósidos y linezolid se ha asociado con la colonización por EPC. **Implicaciones:** Identificamos variables asociadas con la colonización de EPC en pacientes oncológicos. Nuestros resultados pueden indicar acciones para prevenir la colonización de CPE y el consiguiente desarrollo de infecciones.

DESCRIPTORES

Resistencia a Múltiples Medicamentos; Control de Infecciones; Factores de Riesgo; Enterobacteriaceae Resistentes a los Carbapenémicos.

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There are no conflicts of interest to declare.