American Journal of Infection Control 47 (2019) 213–216

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Brief Report

Incidence and predictors of health care–associated infections among patients colonized with carbapenem-resistant Enterobacteriaceae

Adriana Aparecida Feltrin Correa MSc [a,b], Carlos Magno Castelo Branco Fortaleza MD, PhD [a,*]

[a] Department of Tropical Diseases, Botucatu Medical School, São Paulo State University (UNESP), City of Botucatu, São Paulo State, Brazil
[b] Bauru State Hospital, São Paulo State Health Department. City of Bauru, São Paulo State, Brazil

Key Words:
Carbapenem-resistant
Enterobacteriaceae
Colonization
Healthcare-associated infections

Colonization with carbapenem-resistant Enterobacteriaceae (CRE) precedes invasive infections. Neither the actual risk for the latter nor the route between the 2 stages is completely clear. We studied a retrospective cohort of patients hospitalized between 2013-2016 and colonized with CRE. The incidence of CRE health care–associated infections was 13.2%, and predictors were the presence of a urinary catheter and the use of carbapenems. Infection prevention strategies in CRE-colonized patients should focus on invasive devices and antimicrobial stewardship.

© 2018 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

Carbapenem-resistant Enterobacteriaceae (CRE) emerged in the past decade and spread worldwide.[1] They are presently one of the most challenging threats to patient safety in many countries, including Brazil.[2] Infections caused by CRE have few therapeutic options and attributable mortality rates reaching 44%.[3]

Patients colonized with CRE contribute to the spread of this agent within health care settings.[4] They are also at greater risk for development of invasive infections.[5] In hospitals that perform active search through surveillance cultures, those colonized persons can be identified and placed under contact precautions. Importantly, those cultures also identify cohorts of patients for whom special care should be taken to prevent health care–associated infections (HCAIs). The identification of predictors for CRE-HCAIs among colonized patients may be helpful in directing preventive measures for this population.

METHODS

We studied a nonconcurrent (retrospective) cohort of CRE-colonized patients in Bauru State Hospital (350 beds), a tertiary care facility in the city of Bauru, inner Brazil. In that hospital, CRE was first reported in February 2013. Since then, surveillance cultures (rectal swabs) were collected in the following situations: (1) on admission and weekly for patients in intensive care units (ICUs) and burn wound wards; (2) on admission for patients transferred from other hospitals; (3) for all patients in units in which a case of colonization or infection was detected.

The study enrolled patients admitted to the hospital in years 2013 through 2016. Inclusion criteria for the cohort were (1) a positive surveillance culture in the absence of infection (either community or health care–associated) and (2) an "autochthonous" colonization (ie, the first positive surveillance culture was collected 48 hours after admission). Any positivity in clinical cultures within 24 hours of the surveillance culture was a criterion for exclusion of the cohort. The outcome of interest was the acquisition of CRE-HCAI, defined as a patient meeting National Healthcare Safety Network surveillance definitions[6] for any HCAI plus clinical culture from specimens in the infection site positive for CRE (the same species found in surveillance cultures).

An extensive chart review was performed to record demographic data, comorbidities (including the Charlson Comorbidity score[7]), invasive procedures, devices, and use of antimicrobials. "Time of follow-up" was defined as days counted from the date of first positive surveillance culture up to the day of CRE-HCAI diagnosis or discharge from the hospital. Statistical analysis was performed with SPSS 20 (IBM, Armonk, NY). Univariate and multivariable models of Cox regression were used to identify predictors for the outcome of interest, with censoring performed at discharge/death. In the multivariable step, a forward strategy of variable selection was applied, with P values = .05 and .10 for inclusion and removal of variables in the models. Kaplan-Meier survival curves (with log-rank test) were used for graphic expression of independent predictors.

* Address correspondence to Carlos Magno Castelo Branco Fortaleza, MD, PhD, Departamento de Doenças Tropicais - Faculdade de Medicina de Botucatu, Distrito de Rubião Júnior, S/N, City of Botucatu, São Paulo State Brazil, 18618-970.
E-mail address: cmfortaleza@uol.com.br (C.M.C.B. Fortaleza).

Funding/support: C.M.C.B.F. received a researcher grant from the National Council for Scientific and Technological Development (CNPq, process 312149/2015-8), Brazil.
Conflicts of interest: None to report.

https://doi.org/10.1016/j.ajic.2018.08.007
0196-6553/© 2018 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

Table 1
Univariate and multivariable Cox regression analysis of predictors of progression of carbapenem-resistant Enterobacteriaceae colonization to health care–associated infections

Risk factors	Cohort characteristics (384 subjects)	Univariate analysis HR (95% CI)	*P*	Multivariable analysis HR (95% CI)	*P*
Demographic data					
Female sex	145 (37.8)	1.41 (0.81-2.44)	.23		
Age, median (quartiles)	61 (45-73)	1.00 (0.99-1.02)	.60		
Comorbidities					
Heart disease	117 (30.5)	1.52 (0.87-4.23)	.08		
Pulmonary disease	202 (52.6)	1.52 (0.87-2.66)	.14		
Renal disease	134 (34.9)	0.91 (0.51-1.64)	.76		
Liver disease	29 (7.6)	0.69 (0.21-2.23)	.53		
Diabetes mellitus	87 (22.7)	1.03 (0.52-2.07)	.93		
CNS disease	84 (21.9)	1.10 (0.59-2.05)	.76		
Solid malignancy	51 (13.3)	1.76 (0.89-3.47)	.10		
Lymphoma/leukemia	7 (1.8)	1.37 (0.19-9.96)	.76		
AIDS	8 (2.1)	0.64 (0.08-4.66)	.66		
Trauma	11 (2.9)	0.05 (0.00-178.58)	.47		
Charlson comorbidity score	3 (1-5)	1.08 (0.98-1.19)	.11		
Admission data					
Transfer from other hospital	232 (60.2)	0.89 (0.51-1.70)	.69		
Previous time of admission*	11 (6-19)	0.99 (0.98-1.01)	.65		
Admission to ICU	269 (70.1)	1.99 (0.93-4.23)	.08		
Neutropenia†	38 (9.9)	1.15 (0.49-2.72)	.75		
Use of steroids	151 (39.3)	0.98 (0.56-1.17)	.93		
Invasive procedures/devices					
Surgery	141 (36.7)	1.60 (0.90-2.84)	.11		
Surgical drains	20 (5.2)	1.37 (0.48-3.35)	.56		
Mechanical ventilation	**203 (52.9)**	**2.95 (1.47-5.90)**	**.002**		
Central venous catheter	**252 (65.6)**	**3.72 (1.47-9.39)**	**.005**		
Urinary catheter	**276 (71.9)**	**7.57 (1.84-31.21)**	**.005**	**5.56 (1.31-23.63)**	**.02**
Use of antimicrobials					
Penicillins	6 (1.6)	0.90 (0.12-6.50)	.91		
Penicillins + B-lactamase inhibitors	102 (26.6)	0.68 (0.35-1.30)	.24		
Cephalosporins, 1st/2nd generations	12 (3.1)	0.61 (0.08-4.45)	.63		
Cephalosporins, 3rd/4th generations	80 (20.8)	1.66 (0.93-2.96)	.09		
Carbapenems	**135 (35.1)**	**2.49 (1.38-4.50)**	**.002**	**1.96 (1.06-3.62)**	**.03**
Glycopeptides	105 (27.3)	1.61 (0.92-2.82)	.10		
Quinolones	33 (8.6)	0.79 (0.28-2.19)	.65		
Aminoglycosides	**34 (8.9)**	**1.95 (1.02-3.72)**	**.04**		
Antianaerobe drugs‡	37 (9.6)	1.66 (0.80-3.42)	.17		
Antifungals	60 (15.6)	1.81 (1.00-3.27)	.05		

NOTE. Cohort characteristics are presented in number(%), except when specified. Bold values are statistically significant ($P < .05$).
CI, confidence interval; *CNS*, central nervous system; *HR*, hazard ratio; *ICU*, intensive care unit.
*Time of hospital admission before the diagnosis of colonization.
†Any neutrophil count $<500/mm^3$ during follow-up.
‡Clindamycin and metronidazole.

RESULTS

We enrolled 384 CRE-colonized patients into the cohort. Microorganisms isolated were *Klebsiella pneumoniae* (85.7%), *Enterobacter* spp (13.3%), and *Escherichia coli* (1.0%). Among those patients, 51 (13.2%) progressed to CRE-HCAIs (incidence density, 7.3 per 1,000 colonized hospitalization days). The incidence of infection was 16.0% (8.4 per 1,000 colonized hospitalization days) in ICUs and 7.0% (4.3 per 1,000 colonized hospitalization days) in other wards ($P = .02$). The median time from colonization to infection was 11 days (range, 2 to 174 days). Infection sites were distributed as follows: urinary tract infections (n = 20 patients), pneumonia (n =14), bloodstream infections (n = 13), surgical site infections (n = 2), and skin and soft tissue infections (n = 2).

Table 1 presents univariate and multivariable analysis of predictors of CRE-HCAIs in the cohort. Briefly, the presence of a urinary catheter and the use of carbapenems were independently associated with the outcome of interest. Survival curves for those predictors are presented in Figure 1.

DISCUSSION

Colonization has long been recognized as a stage preceding infection.[8] However, neither the actual risk for the latter nor the route between the 2 stages is completely clear. Actually, those aspects may vary between outbreaks and endemic settings.[5,9]

Our study was conducted in a setting of recent emergence and rapid progression to hyperendemicity—a picture that is frequent among hospitals in Brazil and other countries.[2] Our findings may be applicable to similar settings.

The incidence of CRE-HCAIs in the cohort was 13.2%. A recent systematic review reported an aggregate risk of 16.5%.[5] That review is limited by relevant heterogeneity among studies—regarding population characteristics and admission settings. Not surprisingly, the incidence of HCAIs in those studies ranged from 0%-89%. It is worth noting that our result may be underestimated by our outcome definitions. In requiring a clinical culture positive for CRE, we valued specificity over sensitivity.

Predictors in the cohort are coherent with the infection sites. The association of urinary catheter and CRE-HCAIs was expected, because nearly 40% of detected infections were urinary tract infections. The finding regarding use of carbapenems is less straightforward. One should notice that this association was detected for the use of carbapenem after the diagnosis of colonization, and therefore it is not due to the fact that carbapenems are usual risk factors for CRE acquisition.[1,4] Instead, it points to a role of antimicrobials in the progression of colonization to infection. A possible explanation is the elimination of competing pathogens, leading to an increase in bacterial load and

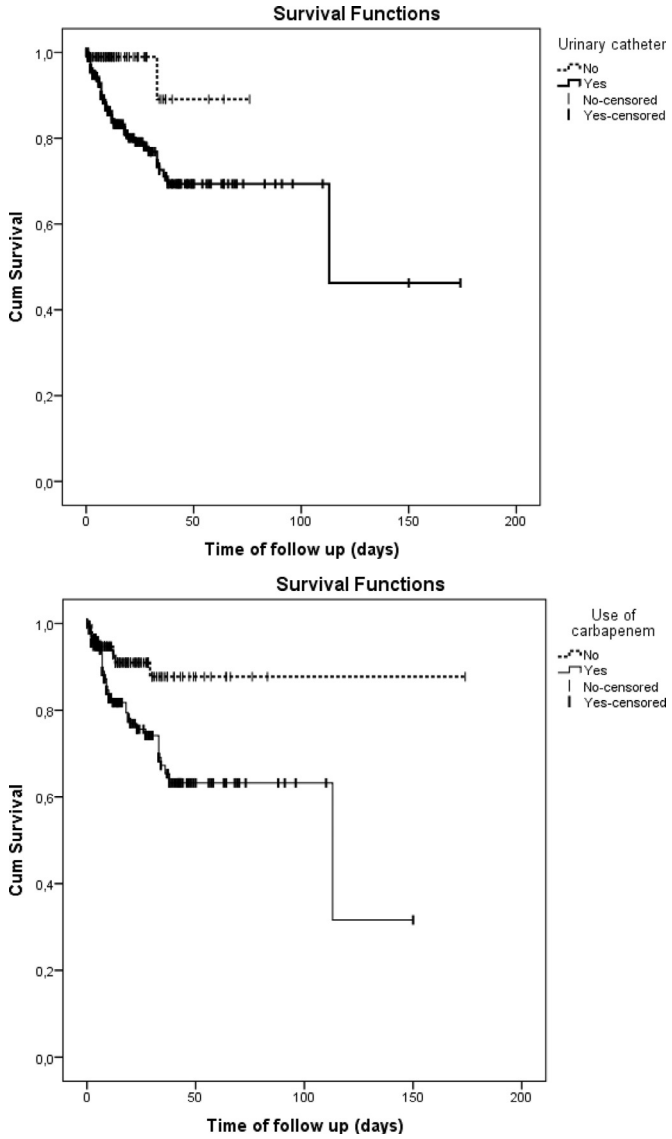

Fig 1. Survival curves (Kaplan-Meier) for significant predictors of carbapenem-resistant Enterobacteriaceae colonization to health care–associated infections: (A) Insertion of urinary catheter; (B) use of carbapenems. Note that in log-rank test, $P = .001$ for both predictors.

CRE invasiveness.[10] But we cannot rule out the possibility that carbapenem use was a proxy of severity of illness or other risk factor not addressed in the study.

One limitation of our study was the lack of strain typing, which could associate more conclusively clones causing colonization and infection. Also, the rules for collecting rectal swabs in our institution may have influenced results, especially by overinclusion of ICU patients. We did not perform surveillance for postdischarge infections, so our incidence may have been underestimated. Finally, we did not perform competing-events analysis and did not adjust results for usual severity-of-illness scores, such as the Acute Physiology and Chronic Health Evaluation II, the Simplified Acute Physiology Score II, or others. However, we did adjust results for the Charlson Comorbidity Index, which has been regarded as a proxy indicator of the severity of illness and the risk of death. There are also strengths in our study. Our cohort was larger than those reported in most studies included in the systematic review cited above,[5] and we performed extensive analysis of potential risk factors.

In conclusion, a relevant proportion of CRE-colonized patients will progress to infection. Predictors for that outcome were the presence of a urinary catheter and the use of carbapenems. Infection prevention strategies in CRE-colonized patients should include special attention to invasive devices. Antimicrobial stewardship, preventing overuse of carbapenems, may also contribute to prevent CRE-HCAIs in that population.

References

1. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J Infect Dis 2017;215 (suppl 1):S28-36.
2. Sampaio JL, Gales AC. Antimicrobial resistance in Enterobacteriaceae in Brazil: focus on β-lactams and polymyxins. Braz J Microbiol 2016;47(Suppl 1):31-7.
3. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerg Infect Dis 2014;20:1170-5.
4. Friedman ND, Carmeli Y, Walton AL, Schwaber MJ. Carbapenem-resistant Enterobacteriaceae: a strategic roadmap for infection control. Infect Control Hosp Epidemiol 2017;38:580-94.
5. Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: a systematic review. Am J Infect Control 2016;44:539-43.

6. National Healthcate Safety Network. CDC/NHSN Surveillance Definitions for Specific Types of Infections. Atlanta (GA): CDC, 2018.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
8. Jarvis WR. The epidemiology of colonization. Infect Control Hosp Epidemiol 1996;17:47-52.
9. McConville TH, Sullivan S, Gomez-Simmonds A, Whittier S, Uhlemann AC. Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study. PLoS One 2017;12:e0186195.
10. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. Emerg Infect Dis 2002;8:347-54.

Coming Soon in AJIC

A program to improve the hand hygiene compliance of Hong Kong preschoolers with an insight into their absenteeism

Nosocomial outbreak of influenza A H3N2 in an inpatient oncology unit related to health care workers presenting to work while ill

Compliance with evidence-based guidelines for the prevention of Central Line Associated Bloodstream Infections in a Belgian home care setting: an observational study