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Carbapenem resistance in Enterobacterales bloodstream infections among children with cancer or post-haematopoietic stem cell transplant: a retrospective cohort study

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Background: Risk factors for carbapenem resistance in Enterobacterales bloodstream infections among children with cancer or post-HSCT have not been thoroughly explored.

Methods: All children with cancer or post-HSCT who developed Enterobacterales bloodstream infections in two cancer referral centres in major Colombian cities between 2012 and 2021 were retrospectively examined. When the infection episode occurred, carbapenem resistance mechanisms were evaluated according to the available methods. Data were divided in a training set (80%) and a test set (20%). Three internally validated carbapenem-resistant Enterobacterales (CRE) prediction models were created: a multivariate logistic regression model, and two data mining techniques. Model performances were evaluated by calculating the average of the AUC, sensitivity, specificity and predictive values.

Results: A total of 285 Enterobacterales bloodstream infection episodes (229 carbapenem susceptible and 56 carbapenem resistant) occurred [median (IQR) age, 9 (3.5–14) years; 57% male]. The risk of CRE was 2.1 times higher when the infection was caused by *Klebsiella* spp. and 5.8 times higher when a carbapenem had been used for ≥3 days in the previous month. A model including these two predictive variables had a discriminatory performance of 77% in predicting carbapenem resistance. The model had a specificity of 97% and a negative predictive value of 81%, with low sensitivity and positive predictive value.

Conclusions: Even in settings with high CRE prevalence, these two variables can help early identification of patients in whom CRE-active agents are unnecessary and highlight the importance of strengthening antibiotic stewardship strategies directed at preventing carbapenem overuse.

Introduction

Antimicrobial resistance has emerged as a global threat.[1,2] Of the different resistant bacteria, carbapenem-resistant Enterobacterales (CRE), *Pseudomonas* spp. and *Acinetobacter* spp. are the greatest threat to human health according to the WHO.[3] CRE infections are capable of global rapid spread,[4] and episodes are increasingly noted in children.[5] However, the epidemiology, risk factors and outcome data of paediatric CRE infections have not been thoroughly explored.

The growing number of children with a weakened immune system has led to a high frequency of bloodstream infection (BSI) worldwide.[6,7] These patients have a high risk of mortality, which worsens when inappropriate empirical antibiotics are used, especially for Gram-negative pathogens.[8] Given that antibiotics against CRE are not routinely used empirically in immunocompromised children,[9] identifying the risk factors of CRE in children who have findings suggestive of BSI is crucial to guide empirical therapy and reduce negative short- and long-term outcomes, including mortality.

Reports on the risk factors for CRE in adult patients have been recently published,[10] but those in children are limited. Case–control studies have been conducted in children to identify risk factors for infection or colonization with carbapenem resistance (CR); however, BSI episodes have seldom been included.[11,12] In addition, while an immunocompromised status is a risk factor for CRE in children and adults,[13,14] detailed risk factors for CRE among immunocompromised children who develop BSI have not been described. Therefore, this study aimed to understand the aetiology of episodes of bacteraemia caused by Enterobacterales in different Colombian cancer referral centres and identify risk factors for CRE among these episodes.

Methods

Study design and setting

This retrospective cohort study was conducted in two cancer centres in two major cities in Colombia. These hospitals were Hospital La Misericordia in Bogotá (HOMI) and Clínica Imbanaco Grupo Quironsalud in Cali (CI), which have a paediatric bed capacity of 500 and 110 and care for 250 and 60 paediatric patients with newly diagnosed cancer each year, respectively.

Patients were identified from laboratory databases and were included if they had BSI caused by any Enterobacterales species between 2015 and 2019 in HOMI, or 2012 and 2021 in CI. Using a standardized data collection form, physicians trained in infectious diseases collected patient data retrospectively from the medical records. Data were collected intermittently, at intervals of a maximum of 6 months, throughout the study period. The case recollection form and study protocol were reviewed and approved by the local institutional review board of each participating centre, with informed consent waived.

Participants

Patients were included if they were aged below 18 years, were diagnosed with cancer (haematological or solid), with or without neutropenia, or had received an HSCT and developed BSI (irrespective of the source) caused by any Enterobacterales species. Those with a second episode of bacteraemia with the same bacterium were included if more than 3 months had elapsed after the first episode. Episodes caused by different bacteria were included if more than 1 month had elapsed after the first episode.

Explanatory and outcome variables

During the study period, all inpatient blood cultures with Gram-negative isolates were identified by VITEK® MS (bioMérieux, Marcy-l'Étoile, France). Susceptibility was tested according to the manufacturer's recommendations using AST272 for blood culture samples in the VITEK® 2XL system (bioMérieux). Enterobacterales were classified according to their antibiotic susceptibility profile. As per the CLSI criteria, bacteria identified during the BSI were classified as third-generation cephalosporin susceptible (3GC-S), third-generation cephalosporin resistant but susceptible to carbapenems (3GC-R) or CR. CRE was defined according to the CDC.[15] The 3GC-S and 3GC-R were further classified as carbapenem-susceptible Enterobacterales (CSE) with MIC $\leq$ 1 mg/L for imipenem, doripenem or meropenem, or MIC $\leq$ 0.5 mg/L for ertapenem.[16]

Exposure data included demographic and clinical information, including baseline conditions and recent exposure histories. Patients transferred from another facility or those who entered the bone marrow transplant unit were evaluated for rectal colonization using CHROMID® CARBA SMART (bioMérieux, Marcy-l'Étoile, France). Patient outcomes included ICU requirement and duration caused by bacteraemia, duration of fever, and mortality caused by bacteraemia.

Hospital-acquired infection (HAI) and neutropenia were defined previously.[17] Mortality was considered to be BSI related if occurring without clinical recovery from sepsis-associated organ dysfunction.

Resistance mechanisms among CRE

The presence of carbapenemases in CRE was explored according to the available technology during the BSI episode at different study sites. From the beginning of the study period until 2017, the centres evaluated the presence of carbapenemases by using the Hodge test, double-disc methods with boronic acid and EDTA, or a combination of these techniques. Since 2017, carbapenem-non-susceptible isolates have been further processed to determine the presence of carbapenemases using the RAPIDEC® CARBA NP (bioMérieux, Marcy-l'Étoile, France), and since 2018, blood cultures that detected a Gram-negative pathogen have been considered as candidates for evaluation by the BIOFIRE® blood culture identification 2 (BCID2) panel (bioMérieux, Marcy-l'Étoile, France) according to the attending physician's considerations. Throughout the study period at CI, a strain repository was maintained at −20°C for some bacterial isolates with MDR phenotypes. Finally, the presence or absence of CR-associated bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA} and bla_{IMP} genes in the available strains from the biorepository was determined using the Xpert® Carba-R (Cepheid, Sunnyvale, CA, USA).

Sample size

A 2014 cross-sectional pilot study conducted at CI detected that 15% of Enterobacterales cases were CRE. In addition, approximately 10%–20% of *Klebsiella pneumoniae* isolates in Colombia are CR.[18] Therefore, we calculated that at least 200 episodes of Enterobacterales bacteraemia were required to detect a CRE prevalence of 15%, with 95% confidence and 5% precision. Moreover, a minimum of 10 events of interest per explanatory variable is recommended.[19] In the final model, each of the two explanatory variables had 28 events of interest (CRE), allowing precise and unbiased estimates of regression coefficients.

Data analysis

Qualitative variables are presented as frequencies and percentages, and quantitative variables as means and SD or medians and IQR. The fit to normal distribution was assessed by the Shapiro–Wilk test. A bivariate logistic regression analysis was conducted to compare CRE and CSE

episodes. Strength of associations between explanatory variables and CRE were quantified by OR and 95% CI. Cluster standard errors were estimated to adjust for possible correlation between episodes in the same patient. Variables significant at a *P* value of <0.05 were selected as potential risk factors for CRE.

Subsequently, CRE prediction models were created based on the potential risk factors identified in the bivariate analysis. Initially, data were divided in a training set (80%) and a test set (20%). Three models were created: one was a multivariate logistic regression model, which was estimated using a backward selection algorithm based on the Akaike information criterion and the other two used data mining techniques (a decision tree and a random forest algorithm). To obtain internal validation of the models, we conducted a repeated k-fold cross-validation procedure by using a k-fold of 10 and 5 replicates. Each subset was generated by a stratified selection to ensure the same ratio of CRE and CSE cases in each k-subset. Model performances were evaluated by calculating the average of the AUC, sensitivity, specificity and predictive values. These metrics were also quantified in the test set. The goodness of fit for the logistic model was evaluated using the likelihood ratio test and model deviance, and the Hosmer–Lemeshow test. Both decision tree with classification and regression tree (CART) and random forest models were built using the same subset of potential risk factors used in logistic regression. These models were used to classify each sample as CSE or CSE based on potential risk factors. Therefore, both approaches offered a direct prediction without using a score or percent probabilities.

Models including and excluding aetiology as an explanatory variable were explored, to be applied in clinical practice according to the availability of preliminary results from the microbiology laboratory. A description of different outcomes according to susceptibility profiles was performed. The impact of CRE infection on ICU admission or mortality risk was adjusted for age, sex, high-risk leukaemia (myeloid leukaemia, induction ALL, rescue therapy), history of ICU admission, aetiology and days of neutropenia in a multivariate logistic regression analysis. Analyses were performed in STATA (version 17.0, StataCorp, TX, USA) and the R.4.2.2 software using the package *caret*.

Results

Baseline characteristics of the study population and differences between CRE and CSE episodes

Within the study period, 285 Enterobacterales BSI episodes occurred in 274 children with cancer or post-HSCT. Their median (IQR) age was 9 (3.5–14) years, and 162 (57%) were male. Table 1 presents the demographic and clinical characteristics of these patients and their BSI episodes.

We found 229 BSI episodes caused by CSE (131 were 3GC-S; 98 were 3GC-R) and 56 episodes of CRE BSI. The most frequently isolated Enterobacterales among the CRE isolates was *Klebsiella* spp. ($n=30$; 53.6%), followed by *Escherichia coli* ($n=16$; 28.6%). The aetiology differed between CRE and CSE, and between 3GC-S, 3GC-R and CR (Figures S1 and S2, available as Supplementary data at *JAC* Online).

While there were no significant differences in baseline conditions, antibiotic exposure, especially carbapenems, for more than 72 h in the previous month was more frequent in those who experienced CRE episodes, whereas cefepime, fluoroquinolones, piperacillin/tazobactam or third-generation cephalosporins showed no significant difference. Patients who developed CRE had higher C-reactive protein levels at baseline (Table 1).

Differences in similar variables were observed between 3GC-S, 3GC-R and CR episodes (Table S1).

Independent risk factors for CR among patients with Enterobacterales BSIs

Multivariate logistic regression, decision trees and random forest models were created to examine the independent risk factors for CR among patients with Enterobacterales BSI. Models were created with and without the BSI aetiology. In this way, they could be applied clinically according to the availability of preliminary aetiological reports from the microbiology laboratory. In the training set of the logistic regression model that included BSI aetiology, the risk of CRE was 2.1 times higher when the infection was caused by *Klebsiella* spp. and 5.8 times higher when a carbapenem had been used for ≥3 days in the previous month. A model that included these two predictive variables or risk factors had a discriminatory performance of 77% in differentiating CRE from CSE in the test set. The model had a sensitivity of 18%, specificity of 96%, positive predictive value (PPV) of 50% and negative predictive value (NVP) of 83% (Table 2). Overall, logistic regression models had a better fit for the data and higher AUC in the internal validation procedure using repeated k-fold cross-validation (Table S2). In this cohort, all BSI episodes with both risk factors had a CRE (Figure S3).

The logistic regression performed better than the decision trees and random forest in the models that excluded data on BSI aetiology (Table S2). In the logistic regression model, the only risk factor for CRE was the use of a carbapenem for ≥3 days in the previous month. In the test set, this model correctly identified a CRE case in 72% of cases with high specificity (100%) but low sensitivity (9%) (Table 2).

Evolution over time

Figure 1 depicts the similar trends over time of CRE and CSE and the rates of mortality, carbapenem-resistant *Klebsiella* spp. among all Enterobacterales BSI episodes, and carbapenem use for ≥3 days among all patients who used carbapenems.

Outcomes

Patients with CRE had poorer outcomes than patients with CSE. Overall, a large proportion of patients required ICU admission, and the mortality rate was high, especially for patients with CRE (36% versus 14% among patients with CSE, $P=0.001$). Patients with CRE also remained febrile for longer than patients with CSE (Table 3). Similar trends of increased severity were observed according to increasing resistance among the episodes of 3GC-S, 3GC-R and CR (Table S3).

Mechanisms of resistance in CRE

Of the 56 CRE BSI episodes, 52 (93%) were evaluated for carbapenemase presence. The Hodge test was performed in six episodes, all resulting in possible carbapenemase production; double-disc diffusion method with boronic acid and EDTA was performed in 29 episodes, all having the possible production of KPC; and RAPIDEC® CARBA NP was used in 16 episodes, with 14 suggestive of carbapenemase production, 1 negative and 1 (also tested with boronic acid) suggestive of KPC production. One episode was tested using FilmArray®, with positive results for bla_{KPC} production. Of the 13 strains

Table 1. Characteristics of BSI episodes according to the susceptibility profile

Variable	Total $N=285$ *n* (%)	CSE $N=229$ *n* (%)	CRE $N=56$ *n* (%)	OR (95% CI)	*P* value
Age of patient, years, median (IQR)	9.0 (3.5–14.0)	9.0 (3.0–14.0)	10.5 (5.0–14.7)	1.02 (0.97–1.08)	0.40
Sex					
Female	123 (43.2)	103 (45.0)	20 (35.7)	Ref.	
Male	162 (56.8)	126 (55.0)	36 (64.3)	1.47 (0.80–2.70)	0.21
History of HSCT					
No	192 (67.4)	152 (66.4)	40 (71.4)	Ref.	
Yes	93 (32.6)	77 (33.6)	16 (28.6)	0.79 (0.42–1.47)	0.46
Days post-HSCT, median (IQR)	49 (11–132.5)	49 (11.5–138.5)	44 (8.2–98.5)	0.99 (0.99–1.00)	0.96
Time post-HSCT					
No	192 (67.4)	152 (66.4)	40 (71.4)	Ref.	
1–50 days	51 (17.9)	42 (18.3)	9 (16.1)	0.81 (0.37–1.80)	0.61
>50 days	42 (14.7)	35 (15.3)	7 (12.5)	0.76 (0.31–1.85)	0.55
Baseline condition					
HSCT	93 (32.6)	77 (33.6)	16 (28.6)	Ref.	
Induction ALL	56 (19.6)	41 (17.9)	15 (26.8)	1.76 (0.80–3.87)	0.16
Myeloid leukaemia	25 (8.8)	17 (7.4)	8 (14.3)	2.26 (0.92–5.56)	0.07
Immune dysregulation[a]	16 (5.6)	10 (4.4)	6 (10.7)	2.89 (0.92–9.03)	0.07
Solid tumour	36 (12.6)	32 (14.0)	4 (7.1)	0.60 (0.18–1.94)	0.40
Rescue therapy[b]	28 (9.8)	23 (10.0)	5 (8.9)	1.05 (0.31–3.51)	0.94
Consolidation or maintenance	29 (10.2)	28 (12.2)	1 (1.8)	0.17 (0.02–1.37)	0.10
Other	2 (0.7)	1 (0.4)	1 (1.8)	4.81 (0.28–81.22)	0.28
Aetiology					
E. coli	128 (44.9)	112 (48.9)	16 (28.6)	Ref.	
Klebsiella spp.	104 (36.5)	74 (32.3)	30 (53.6)	2.84 (1.44–5.59)	0.003
Enterobacter spp.	35 (12.3)	28 (12.2)	7 (12.5)	1.75 (0.65–4.71)	0.27
Serratia	11 (3.9)	8 (3.5)	3 (5.4)	2.62 (0.63–10.93)	0.19
Proteus	2 (0.7)	2 (0.9)	0 (0.0)	—	—
Salmonella	5 (1.7)	5 (2.2)	0 (0.0)	—	—
Neutropenia[c]					
No	80 (28.1)	68 (29.7)	12 (21.4)	Ref.	
Yes	205 (71.9)	161 (70.3)	44 (78.6)	1.55 (0.77–3.12)	0.22
Days of neutropenia before the BSI,[d] median (IQR)	4 (0–12.5)	2 (0–10)	7.5 (1.2–22.7)	1.02 (1.01–1.04)	0.004
Hospital-acquired infection					
No	45 (15.8)	42 (18.3)	3 (5.4)	Ref.	
Yes	240 (84.2)	187 (81.7)	53 (94.6)	3.97 (1.18–13.38)	0.03
History of BSI in the previous month					
No	220 (77.2)	184 (80.3)	36 (64.3)	Ref.	
Yes	65 (22.8)	45 (19.7)	20 (35.7)	2.27 (1.20–4.30)	0.01
History of ICU admission[e]					
No	198 (69.5)	165 (72.0)	33 (58.9)	Ref.	
Yes	87 (30.5)	64 (28.0)	23 (41.1)	1.80 (0.96–3.35)	0.07
History of infection or rectal colonization[f] with carbapenem-resistant bacteria in the previous 6 months					
No	262 (91.9)	212 (92.6)	50 (89.3)	Ref.	
Yes	23 (8.1)	17 (7.4)	6 (10.7)	1.50 (0.56–3.96)	0.42
Antibiotic exposure[g]					
No	81 (28.4)	74 (32.3)	7 (12.5)	Ref.	
Yes	204 (71.6)	155 (67.7)	49 (87.5)	3.34 (1.45–7.71)	0.005
Use of carbapenems in the previous month					
No	160 (56.1)	146 (63.8)	14 (25.0)	Ref.	

Continued

Table 1. *Continued*

Variable	Total $N=285$ *n* (%)	CSE $N=229$ *n* (%)	CRE $N=56$ *n* (%)	OR (95% CI)	*P* value
1–2 days	11 (3.9)	9 (3.9)	2 (3.6)	2.32 (0.45–11.9)	0.31
≥3 days	114 (40.0)	74 (32.3)	40 (71.4)	5.64 (2.90–10.97)	<0.001
Use of fluoroquinolones in the previous month					
No	261 (91.6)	214 (93.4)	47 (83.9)	Ref.	
1–2 days	3 (1.0)	0 (0.0)	3 (5.4)	—	—
≥3 days	21 (7.4)	15 (6.6)	6 (10.7)	1.82 (0.66–5.03)	0.25
Use of cefepime in the previous month					
No	186 (65.3)	150 (65.5)	36 (64.3)	Ref.	
1–2 days	9 (3.2)	8 (3.5)	1 (1.8)	0.52 (0.06–4.40)	0.55
≥3 days	90 (31.6)	71 (31.0)	19 (33.9)	1.11 (0.59–2.11)	0.74
Use of piperacillin/tazobactam in the previous month					
No	230 (80.7)	188 (82.1)	42 (75.0)	Ref.	
1–2 days	10 (3.5)	7 (3.1)	3 (5.4)	1.92 (0.47–7.81)	0.36
≥3 days	45 (15.8)	34 (14.8)	11 (19.6)	1.45 (0.66–3.16)	0.35
Use of third-generation cephalosporins in the previous month					
No	270 (94.7)	216 (94.3)	54 (96.4)	Ref.	
1–2 days	3 (1.0)	3 (1.3)	0 (0.0)	—	—
≥3 days	12 (4.2)	10 (4.4)	2 (3.6)	0.80 (0.17–3.75)	0.78
Length of antibiotic use in the month prior to BSI onset (days) median (IQR)					
Carbapenem	10 (6–14)	10 (6–14)	13.5 (6.7–14.2)	1.03 (0.98–1.09)	0.17
Fluoroquinolone	7.5 (4.2–11.0)	9 (5–12)	5 (2–10.5)	0.87 (0.72–1.04)	0.13
Cefepime	7 (4–10)	7 (4–10)	6.5 (4–9.5)	0.97 (0.87–1.08)	0.59
Piperacillin/tazobactam	7 (3–10)	7 (4–9.5)	6.5 (2.7–10.2)	0.97 (0.84–1.11)	0.64
Third-generation cephalosporin	4 (3–8)	6 (2.5–9)	3.5 (3–4)	0.77 (0.60–1.00)	0.23
CRP value, median (IQR)	54.1 (19.3–136.2)	48.4 (14.1–121.0)	80.5 (41.7–188.2)	1.003 (1.001–1.005)	0.04
Days of hospital stay prior to the BSI, median (IQR)[d]	28 (13–60)	24 (12–54.5)	38 (22.5–73)	1.005 (0.99–1.01)	0.06
Length of hospital stay prior to the BSI[d] *n* (%)					
≤ 28 days	146 (51.2)	126 (55.0)	20 (35.7)	Ref.	
>28 days	139 (48.8)	103 (45.0)	36 (64.3)	2.20 (1.21–3.99)	0.01
Hospital					
CI	177 (62.1)	146 (63.7)	31 (55.3)	Ref	
HOMI	108 (37.8)	83 (36.2)	25 (44.6)	0.71(0.39–1.27)	0.25

CRP, C-reactive protein.
[a]Aplastic anaemia or haemophagocytic lymphohistiocytosis.
[b]Any treatment administered after cancer relapse that aims to induce a new remission allowing patients to undergo HSCT.
[c]Absolute neutrophil count < 500 cells/mm^3 or an absolute neutrophil count that was expected to decrease to <500 cells/mm^3 during the next 48 h.
[d]Over all time.
[e]Admission to the ICU in the previous month for >48 h.
[f]105 BSI episodes had been evaluated for rectal colonization in the previous 6 months.
[g]Exposure to one or more systemic antibiotics for >72 h in the previous month.

recovered from the biorepository for evaluation using the Xpert® Carba-R technology, 10 had *bla*$_{KPC}$, 1 had *bla*$_{NDM}$ and 2 were negative.

Overall, CR was possibly caused by carbapenemase production (CP-CRE) in 51 (98%) of the 52 evaluated episodes. Of the 43 episodes in which the specific CR mechanism was evaluated, 40 (93%) were confirmed or suggestive of KPC production, 1 (2%) had *bla*$_{NDM}$ and 2 (5%) were non-carbapenemase producers.

Discussion

This retrospective multicentre cohort study identified independent risk factors for CRE among children with cancer or post-HSCT with Enterobacterales BSI. Carbapenem use for ≥3 days and *Klebsiella* spp. identification were the only two factors independently associated with CR.

We provided two models to be used according to the moment of patient evaluation and the availability of aetiological

Table 2. Independent risk factors for CR among patients with Enterobacterales BSIs and performance of the multivariate logistic regression model in the test set

Multivariate logistic regression modelling including the aetiology of the BSI			
Training set: CRE ($n=45$) versus CSE ($n=184$)			
Variable	OR	95% CI	*P* value
Aetiology			
Non-*Klebsiella*	Ref.	1.06–4.18	0.03
Klebsiella spp.	2.11		
Use of carbapenem			
<3 days	Ref.	2.79–12.20	<0.001
≥3 days	5.84		
Test set: CRE ($n=11$) versus CSE ($n=45$)			
AUC	0.77		
Sensitivity	0.18		
Specificity	0.96		
PPV	0.5		
NPV	0.83		
Multivariate logistic regression modelling not including the aetiology of the BSI			
Training set: CRE ($n=45$) versus CSE ($n=184$)			
Variable	OR	95% CI	*P* value
Use of carbapenem			
<3 days	Ref.	2.76–11.70	<0.001
≥3 days	5.68		
Test set: CRE ($n=11$) versus CSE ($n=45$)			
AUC	0.72		
Sensitivity	0.09		
Specificity	1		
PPV	0.5		
NPV	0.81		

information (i.e. via MALDI-TOF MS or preliminary reports from the microbiology laboratory). In both scenarios, carbapenem use in the previous month had high specificity; thus, most patients with CSE will be identified as such by low carbapenem use, allowing clinicians to restrict the use of CRE-active agents and infection prevention departments to strengthen antimicrobial stewardship programmes. In contrast, the low sensitivity of the model highlights the challenges to predict CRE and indicate the need for further studies to identify the subset of patients with BSI who require prompt empirical CRE coverage before susceptibility reports become available.

In this study, carbapenems were the only antibiotic class independently associated with CRE. Similarly, a systematic review of 92 studies, mainly including adult patients, reported that carbapenems were the only class frequently associated with carbapenem-resistant Gram-negative bacterial infections.[20] Although no paediatric specific data describing factors associated with CRE in Enterobacterales BSI are available, paediatric studies reported that carbapenem use is associated with CRE colonization or infection[12] or Gram-negative BSI resistant to broad-spectrum antibiotics.[21] Similar to the EURECA study,[10] in this cohort the overwhelming majority of CRE were CP-CRE. While case–control studies have shown an association between CP-CRE and horizontal transmission rather than with carbapenem treatment,[22] and carbapenem exposure as a significant risk factor for non-carbapenemase-producing CRE (non-CP-CRE) versus CP-CRE,[23] we documented a strong, independent association between carbapenem exposure and CRE in this cohort where almost all isolates were carbapenemase producers. Differences in study results may be explained by different selection criteria (different types of infection or colonization in the above cited case–control studies versus only BSI in our cohort), and different patient population, study designs and control groups. The high CP-CRE prevalence in this study occurred in settings where infection control departments implement strict contact precautions for patients infected with MDR pathogens, suggesting that carbapenem exposure is, at least partly, responsible for the clinical expression of CP-CRE. This may occur via incident acquisition of carbapenemases (particularly KPC in this cohort) via *de novo* mutations, or, more likely, through the emergence of resistance by enriching pre-existing gastrointestinal CP-CRE above the threshold of clinical relevance under selective

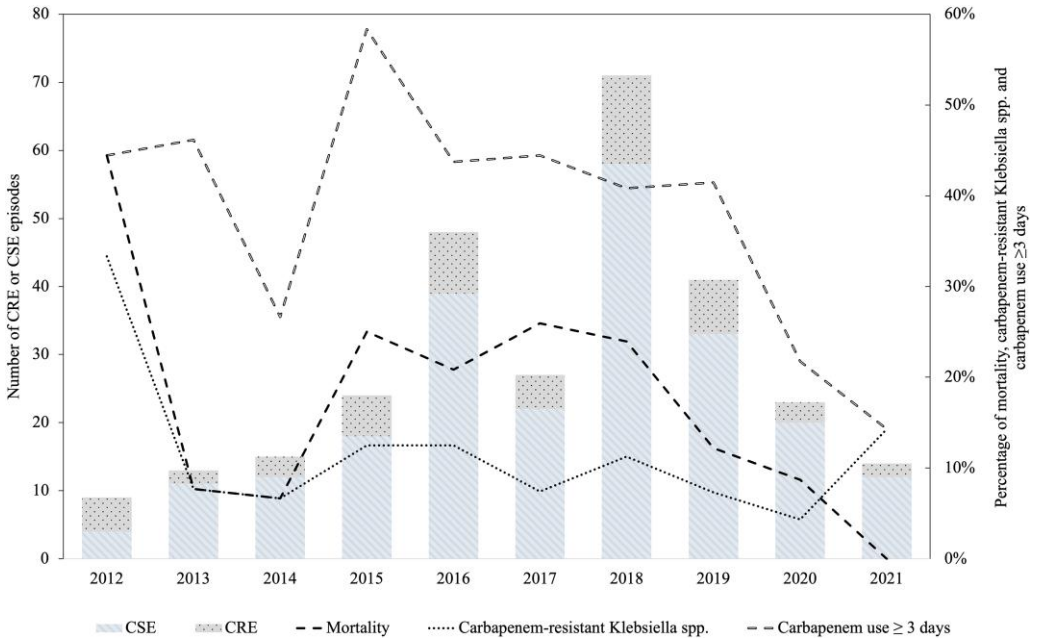

Figure 1. Evolution in the number of Enterobacterales BSI episodes according to susceptibility profiles and rates of mortality, carbapenem-resistant *Klebsiella* spp. among all Enterobacterales BSI episodes, and carbapenem use for ≥3 days among all carbapenem use. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 3. Outcomes of BSI episodes according to susceptibility profiles

Variable	Total $N=285$ n (%)	CSE $N=229$ n (%)	CRE $N=56$ n (%)	P value	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Days of fever associated with the BSI, median (IQR)	2 (1–2)	1 (1–2)	2 (1–4.7)	0.001	—	—
ICU admission due to BSI	95 (33.3)	69 (30.1)	26 (46.4)	0.03	2.01 (1.08–3.73)	1.57 (0.76–3.22)
Days of ICU stay, median (IQR)	8 (4–16)	7.5 (4–15)	9 (4.5–17)	0.34	—	—
BSI-related mortality[b]	53 (18.6)	33 (14.4)	20 (35.7)	0.001	3.30 (1.66–6.56)	2.66 (1.30–5.43)

[a]OR adjusting for age, sex, high-risk leukaemia (myeloid leukaemia, induction ALL, rescue therapy), history of ICU admission, aetiology and days of neutropenia.
[b]Death occurring without clinical recovery from sepsis-associated organ dysfunction.

antibiotic pressure.[24] To further clarify the mechanism of carbapenems in the development of KPC-mediated CP-CRE, it is necessary to study whether carbapenem exposure may enrich the number of endogenous bla_{KPC} gene copies, as it has been documented previously for bla_{NDM-1}.[25]

CR mechanisms and CRE acquisition are heterogeneous in nature,[24] but clearly, antibiotic stewardship strategies, specifically carbapenem overuse prevention, are required to decrease the global health crisis caused by CP-CRE and reduce the poor outcomes and high mortality described in this and other cohorts.[26] The lack of association between short carbapenem exposure and CRE underscores the importance of de-escalation strategies in children with fever and neutropenia. Even if meropenem is started as an empirical therapy, de-escalation to narrower-spectrum antibiotics is important and is associated with a lesser CRE risk compared with longer treatment courses.

Since the emergence of carbapenemases, *Klebsiella* spp., mainly *K. pneumoniae* have been one of the predominant species carrying these resistance genes.[27,28] In our cohort, *Klebsiella* spp. were the most common CRE (54%), consistent with data from the USA and other countries.[10,29–32] *Klebsiella* spp. were identified as an independent risk factor, likely reflecting the increased capacity of this species group to carry plasmids encoding the corresponding resistance enzyme (i.e. bla_{KPC}) compared with other Enterobacterales microorganisms, such as *E. coli*.[31,33] Infection prevention strategies are crucial to avoid the spillover of resistance genes from the *Klebsiella* spp. reservoir to *E. coli* in this population because the latter bacteria spread in the community more readily, and children with cancer and post-HSCT spend their treatment course largely in the ambulatory setting.

Other paediatric studies described previous CRE colonization as a risk factor for colonization or infections in different organ

systems,[29] but this association was not found in our cohort. This discrepancy between studies may be related to having different outcome measures, considering that we only included patients with BSI; in addition, the association may be weaker between previous CRE infection or colonization and BSI, requiring a larger sample size to detect a difference.

According to the results of the training and test datasets, logistic regression performed slightly better than the two data mining models for the prediction of CRE, which may be attributed to the unbalanced ratio between cases with and without CRE (1:4). Unlike decision trees and random forest algorithms, logistic regression models do not assume balanced classes in the training set, more accurately identifying variables relevant to the minority class. However, the unbalanced proportion between groups may also affect logistic regression, creating bias towards the class with a larger number of samples, leading to low sensitivity, as seen in these data.[34]

This study is mainly limited by its retrospective nature. However, the variables included were easily accessible from the medical records, and they were objective and quantifiable and were collected by a restricted group of physicians trained in paediatric infectious diseases that remained constant throughout the data collection period. Although we collected all available information that could clinically or theoretically explain differences between CRE and CSE episodes, the models had low performance, possibly due to unmeasurable variables that may have an effect on carbapenemase production. Given the selection criteria, the study did not evaluate the effect of a CRE BSI on a subsequent BSI shortly after the first episode. However, we evaluated the risk of second CRE BSI episodes occurring between 1 and 12 months or between 3 and 12 months for BSI episodes caused by different or the same bacteria as the original episode, respectively, in patients with an initial CRE BSI compared with an initial CSE BSI. Of the 56 CRE episodes, 2 cases had a subsequent CRE BSI, compared with 6 of 229 CSE BSI (OR 1.36, 95% CI 0.28–6.57, P value = 0.70).

Although this study was conducted in referral institutions from two main cities in Colombia, only one country is represented, limiting the generalizability of results. However, these results may be applied to several other regions worldwide with high CRE prevalence and predominance of KPC carbapenemases as a resistance mechanism among CRE. Also, because of such predominance, these results may be less applicable to BSI caused by non-CP-CRE or by CP-CRE due to non-KPC enzymes. Finally, one of the aspects of model building that may bias the performance of the observed models is the possible correlation between training and test sets, since the splitting of the full dataset was performed after identification of potential high-risk factors. However, we did not find a pattern of overfitting in the AUC, sensitivity and specificity metrics in both datasets.

In conclusion, high CRE prevalence among BSI episodes was associated with poor outcomes in children with cancer and post-HSCT. Our model had high specificity, enabling clinicians and infection prevention departments to limit overuse of CRE-active agents, even in settings with high CRE prevalence. Of all demographic and clinical variables collected, carbapenem use was the only modifiable risk factor; thus, this finding provides additional knowledge essential to combat the growing global threat of CP-CRE. Antibiotic stewardship strategies directed at preventing carbapenem overuse may help to reduce global health inequities due to the large CRE burden in regions with limited access to CRE-active agents.

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Data availability

Deidentified participant data are available with publication by researchers, whose proposed use of the data has been approved and agreed upon by both parties and ethics committees and with a signed data access agreement.

Supplementary data

Figures S1 to S3 and Tables S1 to S3 are available as Supplementary data at *JAC* Online.

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