American Journal of Infection Control 44 (2016) 134-7

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Demographic and infection characteristics of patients with carbapenem-resistant *Enterobacteriaceae* in a community hospital: Development of a bedside clinical score for risk assessment

Brooke M. Miller PharmD [a], Steven W. Johnson PharmD, BCPS [a,b,*]

[a] *Novant Health Forsyth Medical Center, Winston-Salem, NC*
[b] *Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC*

Key Words:
Carbapenem-resistant *Enterobacteriaceae*
CRE
Prediction model
Risk factors
Enterobacteriaceae

Background: The objective of this study was to identify risk factors associated with the presence of carbapenem-resistant *Enterobacteriaceae* (CRE) infections to develop a clinical prediction model that can be used at patient bedside to identify subjects likely infected with a CRE pathogen.

Methods: This case-control study included patients aged ≥18 years admitted to Novant Health Forsyth Medical Center between January 1, 2012, and December 31, 2013, with CRE infections (cases) or non-CRE infections (controls). Controls were matched to their corresponding resistant case (3:1) based on pathogen, place of likely acquisition, isolate source, year of admission, and level of care. A risk prediction model was developed using variables independently associated with CRE isolation. Sensitivities and specificities were obtained at various point cutoffs, and a determination of the receiver operator characteristic (ROC) area under the curve (AUC) was performed.

Results: A total of 164 subjects were included. Independent risk factors for CRE included recent antibiotic therapy, recent immunosuppression, and Charlson Comorbidity Index score ≥4. Adjusted odds ratios were 13.37 (95% confidence interval [CI], 4.16-61.19), 6.69 (95% CI, 1.85-29.65), and 3.30 (95% CI, 1.34-8.40), respectively. Diagnostic performance of various score cutoffs for the model indicated a score ≥5 correlated with the highest accuracy (79%). The ROC AUC was 0.83.

Conclusion: The risk prediction model displayed good discrimination and was an excellent predictor of CRE infection.

Carbapenem-resistant *Enterobacteriaceae* (CRE) have been categorized as an urgent threat level by the Centers for Disease Control and Prevention (CDC). The CDC estimated that there were approximately 9,300 CRE infections resulting in approximately 600 deaths in 2013.[1] The most common types of CRE include carbapenem-resistant *Klebsiella* spp, accounting for 11% of *Enterobacteriaceae* health care–associated infections, and carbapenem-resistant *Escherichia coli*, accounting for 2% of *Enterobacteriaceae* health care–associated infections.[1] Patients infected with CRE are subject to delayed appropriate initial antibiotic therapy (IAT) and, consequently, increased mortality.[2]

To begin appropriate IAT in a timely manner, many health care institutions have recognized the need for risk stratification tools to identify patients at increased risk for infection as a result of CRE organisms. Recent reports have evaluated risk factors for CRE and have proposed various risk factor scoring models; however, these models were created with specific patient populations and organisms.[2-4] Consequently, generalizability and utility in other settings is unknown.

One study examined predictors of carbapenem-resistant *K pneumoniae* acquisition among hospitalized adults. They found that poor functional status, intensive care unit stay, and receipt of antibiotics, particularly fluoroquinolones, were independent risk factors for carbapenem-resistant *K pneumoniae* isolation.[3] This study only identified risk factors for carbapenem-resistant *K pneumoniae*, failing to include other potential CRE-producing organisms. A case-case-control study found that intensive care unit stay and

* Address correspondence to Steven W. Johnson, PharmD, BCPS, Novant Health Forsyth Medical Center, 3333 Silas Creek Pkwy, Winston-Salem, NC 27103.
E-mail address: johnsonsw@campbell.edu (S.W. Johnson).

Previous presentations: This research was previously presented in full as a podium presentation at the Southeastern Residency Conference, April 30, 2015, Athens, GA; and in part as an abstract poster presentation at the American Society of Health-Systems Pharmacy Midyear Clinical Meeting, December 9, 2014, Anaheim, CA.

Conflicts of interest: None to report.

http://dx.doi.org/10.1016/j.ajic.2015.09.006

cumulative number of antibiotic days were independent risk factors of CRE isolation.[4] This study included only nosocomial infections, excluding potential community-acquired CRE. Another study developed a bedside scoring system to differentiate bloodstream infections caused by CRE versus extended-spectrum β-lactamase–producing *Enterobacteriaceae*. They identified neurologic disease, dependent functional status at admission, diabetes mellitus, intensive care unit admission, and antibiotic exposure in 3 months before admission to be risk factors predictive of CRE infection.[2] This study only included patients with severe sepsis, septic shock, or multiorgan failure with bloodstream infections, restricting the use of the scoring system to a small subset of patients.

To our knowledge, no risk prediction model has been published which evaluates all CRE organisms and all sources of infections in hospitalized patients. The primary objective of this study was to identify risk factors associated with the presence of CRE infections at Novant Health Forsyth Medical Center (NHFMC). The secondary objective was to develop a clinical risk prediction model that can be used at patient bedside to identify subjects likely infected with a CRE pathogen to facilitate IAT.

METHODS

This was a retrospective, single-center, case-control study. Potential subjects were identified using the NHFMC infection control database. Subjects were included if they were aged ≥18 years and admitted to NHFMC between January 1, 2012, and December 31, 2013. This study was approved by NHFMC's Institutional Review Board. Cases were defined as patients infected with a CRE obtained from a clinical culture during admission. If >1 isolate was reported for the same patient, only the index culture was included in the study. CRE phenotype was based on Clinical Laboratory Standard Institute–approved methods and interpretive criteria.[5] Controls were defined as patients with *Enterobacteriaceae* (non-CRE) infections. Controls were matched to their corresponding resistant case in a 3:1 fashion based on pathogen, place of likely acquisition (ie, health care associated vs community acquired), isolate source, year of admission, and level of care (ie, critical care vs medicine). Subjects were excluded if the positive culture was thought to represent contamination or colonization (eg, no signs or symptoms of active infection), medical records were incomplete, or a control patient had a prior history of CRE.

Data collection from both electronic and paper-based medical records included patient demographics (age, sex, admission date, admission unit); culture results; antibiotic therapy during the 3 months preceding index culture; hospitalization during the 12 months preceding index hospitalization; transfer from another health care facility; urinary catheterization during the 30 days preceding the index hospitalization; comorbidities included in the Charlson Comorbidity Index[6]; and immunosuppressive drug therapy during the 3 months preceding index culture, defined as glucocorticoids (equivalent to prednisone ≥20 mg for ≥2 weeks), tacrolimus, sirolimus, cyclosporine, mycophenolate, or antithymocyte globulin.

Standard descriptive statistics were used to describe the study cohort and compare cases with controls. Continuous variables were expressed as means and were compared using Student *t* test for normally distributed variables. Categorical variables were analyzed by χ^2 or 2-tailed Fisher exact test. Odds ratio and 95% confidence intervals were calculated to evaluate the strength of any association that emerged. JMP 8 statistical software (SAS Institute, Cary, NC) was used to perform the statistical analyses. A univariate analysis was performed to identify variables significantly more associated with cases than controls (defined as $P < .05$). Variables associated ($P \leq .10$) with CRE isolation in the univariate analysis were then included into a logistic regression model, and a backward stepwise approach was used to identify risk factors for CRE isolation. Variables were kept in the final model if the *P* value was <.05. The final regression model was transformed into a point-based tool with weighted scores assigned to the variables identified to be associated with CRE isolation. The scores assigned to each variable were obtained by dividing each regression coefficient by half of the smallest coefficient and rounding to the nearest integer. The sensitivity, specificity, negative predictive value, and positive predictive value of the prediction tool were expressed at various point cutoffs. A receiver operator characteristic area under the curve (AUC) was performed on the model to determine the model's predictive value.

Table 1
Demographic and infection characteristics of patients with CRE in 2012 and 2013

Characteristic	2012	2013	Total
Patient characteristics			
Age, y	72.3 ± 14.4	63.5 ± 11.2	67.3 ± 13.3
Male	5 (28)	14 (61)	20 (46)
CRE pathogen			
Klebsiella pneumoniae	8 (44)	10 (43)	18 (44)
Enterobacter spp	9 (50)	11 (48)	20 (49)
Citrobacter freundii	1 (6)	0 (0)	1 (2)
Morganella morganii	0 (0)	1 (4)	1 (2)
Proteus mirabilis	0 (0)	1 (4)	1 (2)
Isolate source			
Urinary tract	13 (72)	12 (52)	25 (61)
Skin and soft tissue	3 (17)	3 (13)	6 (15)
Blood	0 (0)	4 (17)	4 (10)
Lower respiratory tract	2 (11)	4 (17)	6 (15)
CRE susceptibility			
Aminoglycoside	13 (72)	13 (48)	26 (58)
Ciprofloxacin	6 (33)	12 (44)	18 (40)
Sulfamethoxazole-trimethoprim	7 (39)	15 (56)	22 (49)
Tigecycline*	1 (50)	3 (43)	4 (44)
Comorbidities			
Charlson Comorbidity Index score	3.6 ± 2.8	3.3 ± 2.0	3.4 ± 2.3
Diabetes	12 (67)	10 (43)	22 (54)
Chronic respiratory disease	6 (33)	10 (43)	16 (39)
Chronic heart failure	8 (50)	3 (13)	11 (27)
Chronic kidney disease	7 (39)	6 (26)	13 (32)
Dementia	5 (28)	2 (9)	7 (17)
Liver disease	2 (11)	6 (23)	8 (20)
Connective tissue disease	2 (11)	4 (17)	6 (15)
Medical history			
Transfer from another health care facility	9 (50)	12 (52)	21 (51)
Recent† urinary catheterization	10 (56)	15 (65)	25 (61)
Recent‡ antibiotic therapy	16 (89)	22 (96)	38 (93)
β-lactam therapy	13 (72)	21 (91)	34 (83)
Fluoroquinolone therapy	5 (28)	9 (39)	14 (34)
Carbapenem therapy	4 (22)	5 (22)	9 (22)
Recent§ hospitalization	17 (94)	20 (87)	37 (90)
Recent‡ immunosuppression	5 (28)	6 (26)	11 (27)
Amputation-paraplegia	3 (17)	3 (13)	6 (15)
Patient admission location			
Medicine unit	8 (44)	9 (39)	17 (41)
Critical care unit	9 (50)	14 (61)	23 (56)
Other units	1 (6)	0 (0)	1 (2)
Location of likely acquisition of CRE			
Hospital or health care associated	17 (94)	20 (87)	37 (90)
Community	1 (6)	3 (13)	4 (10)

NOTE. Values are mean ± SD or n (%).
CRE, carbapenem-resistant *Enterobacteriaceae*.
*Not all cultures tested for susceptibility.
†Within the last 30 days before index hospitalization.
‡Within the last 90 days before obtaining index culture.
§Within the last year before index hospitalization.

RESULTS

A total of 164 subjects (41 cases, 123 controls) were included. Table 1 compares CRE cases isolated in 2012 with CRE cases isolated in 2013. The number of CRE infections increased from 2012 to 2013