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MAJOR ARTICLE

Derivation of a Model to Guide Empiric Therapy for Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infection in an Endemic Area

Gregory Weston,[1] Fathima Jahufar,[2] Nikhil Sharma,[2] Christopher Su,[3] Eran Bellin,[3,4] and Belinda Ostrowsky[1]

[1]Division of Infectious Disease, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, [2]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, [3]Department Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, and [4]Department of Epidemiology and Population Health, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA

Background. Appropriate therapy for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bloodstream infection (BSI) is often given late in the course of infection, and strategies for identifying CRKP BSI earlier are needed.

Methods. A retrospective case–control study was performed at a tertiary care hospital, university hospital, and community hospital in Bronx, New York. All participants had a blood culture sent and received an antibiotic within 48 hours of the culture. The case group (n = 163) had a blood culture with CRKP. The control group (n = 178) had a blood culture with carbapenem-susceptible *Klebsiella*. Data were obtained by electronic or conventional medical record abstraction. A multiple logistic regression model was built to identify associated factors and develop a clinical model for CRKP BSI. Model performance characteristics were estimated using a 10-fold cross-validation analysis.

Results. A prior nonblood culture with carbapenem-resistant Enterobacteriaceae, skilled nursing facility (SNF) residence, mechanical ventilation, and admission >3 days were strongly associated risk factors. A significant interaction led to development of separate clinical models for subjects admitted <3 days at the time of positive blood culture from those admitted at least 3 days. The derived models had a good ability to discriminate between subjects with and without CRKP BSI. A clinical classification rule to guide therapy can prioritize sensitivity or specificity.

Conclusions. Prior nonblood cultures showing resistance and exposure to SNF and health care settings are factors associated with carbapenem resistance. The clinical classification rules derived in this work should be validated for ability to guide therapy.

Keywords. CRE; bacteremia; multidrug resistance; risk factor.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the most prevalent carbapenem-resistant Enterobacteriaceae (CRE) and is an emerging pathogen throughout the world [1]. In the United States, the percentage of *K. pneumoniae* resistant to carbapenem antibiotics increased from 1.6% in 2001 to 10.4% in 2011 [2]. Available therapeutic options for infections with CRKP such as polymyxin and tigecycline carry burdensome side effects and have questionable efficacy [3]. Newer antibiotics such as ceftazidime-avibactam may be more effective [4] but are often reserved for known cases of CRKP infection to minimize development of resistance. Carbapenem-resistant infections have been associated with inappropriate empiric therapy [5], and there is often a delay of days before optimal therapy is started [6]. The mortality associated with CRKP bloodstream infection (BSI) has been reported to be 50% [7].

Prior studies identified health care exposures as potential factors for CRKP infection or colonization. Receipt of antibiotics, residence in a skilled nursing facility (SNF), admission to an intensive care unit, mechanical ventilation, urinary catheterization, recent surgery, longer hospital stays, and diabetes mellitus have been associated with CRKP [8–14]. There are currently few data assessing the independent association of prior cultures that grow carbapenem-resistant Enterobacteriaceae with acute infection by CRKP.

Our objective in this study was to develop a model using readily available clinical data to guide empiric therapy against CRKP BSI. A model to identify patients with carbapenem-resistant infections is difficult to derive in the general inpatient population because of the very low prevalence of carbapenem resistance in this population. However, the prevalence of carbapenem resistance among *Klebsiella pneumoniae* BSI in our institution during the time period of this study was relatively high—18%. In our institution, matrix-assisted laser desorption and ionization–time of flight (MALDI-TOF) technology

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Correspondence: Gregory Weston, MD, 3411 Wayne Ave Suite 4H, Bronx, NY 10467 (gweston@montefiore.org).

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provides rapid species identification in positive blood cultures without susceptibility results. We therefore focused our study on a model to identify *Klebsiella pneumoniae* BSI patients with a relatively high probability of carbapenem resistance. Such patients would be candidates for empiric therapy against CRKP after *Klebsiella pneumoniae* is identified in blood cultures.

METHODS

Setting, Population, and Study Design

Subjects in this study were admitted or seen in the emergency room at 1 of 3 physically distinct hospitals in the Montefiore Health System (Bronx, NY, USA). Beds and discharges in 2014 were as follows in the 3 Bronx hospitals: Moses (647 and 34 887), Weiler (421 and 25 558), Wakefield (325 and 15 917). The Moses and Weiler Divisions are tertiary care university hospitals, whereas the Wakefield Division has a community hospital quality.

Subjects eligible for inclusion in the case and control groups were selected using Looking Glass. Looking Glass Clinical Analytics (Streamline Health, Atlanta, GA, USA) is an interactive software application for the evaluation of health care quality, effectiveness, and efficiency [15]. The system integrates clinical and administrative data sets, allowing nonstatisticians to produce epidemiologically cogent self-documenting reports. Data not obtained from Looking Glass were obtained by conventional review of the scanned medical record. The study was approved by the Institutional Review Board of the Albert Einstein College of Medicine in 2015.

Patients admitted to 1 of the 3 hospitals between January 1, 2009, and May 30, 2014, who had blood culture collected and antibiotics initiated within 48 hours of the blood culture were eligible for study inclusion. We only included patients who received antibiotics early in the course of suspected infection because the goal of the study was to guide choice of antibiotic—not to guide the decision to start antibiotics. Exclusion criteria were age <21 years or inability to review medical records.

The study employed a case–control design. Cases were subjects who grew CRKP in blood culture and received antibiotics within 48 hours of the culture. Only a subject's first CRKP blood culture in this time period was included in the study, so subjects could not have prior CRKP bacteremia by design. Resistance to carbapenem antibiotics was defined using the current Clinical and Laboratory Standards Institute minimum inhibitory concentration for resistance to meropenem or imipenem (the current standard was applied to the isolates from 2009 and 2010 by reviewing the value of the minimum inhibitory concentration) or by positive modified Hodge test. Intermediate isolates were defined as resistant. Control subjects had a blood culture that grew *K. pneumoniae* susceptible to carbapenems (CSKP) and had received antibiotics within 48 hours of that culture. A random sample of eligible control subjects was included in the study to have approximately the same number of controls as cases. The 1:1 ratio of controls to cases was chosen to limit the burden of chart review.

To achieve a power of 80% (alpha = .05) we planned a sample size of 180 cases to detect an odds ratio of 3 for the variable admission from a skilled nursing facility, assuming 5% of subjects admitted from home with *Klebsiella* bloodstream infection had carbapenem resistance. An odds ratio of 3 was chosen based on a study by Borer et al. that found an odds ratio of 3 for rectal colonization with CRKP for subjects admitted from a skilled nursing facility [11].

Predictor Variables

Forty-one variables were analyzed as factors for CRKP BSI. A prior culture with CRE (respiratory, urine, wound, or fluid) in the 180 days before the study blood culture was a variable of primary interest. Age and sex were recorded for each subject. Exposure to health care settings, devices, procedures, antibiotics, proton pump inhibitors [16], and immunosuppressive medications in the 30 days before the study blood culture was recorded. Presence of septic shock at the time of blood culture was recorded. Suspected infectious syndromes were assigned to each subject using modified National Healthcare Safety Network criteria. The syndrome was called "unknown" if clinical information at the time of blood culture did not meet the criteria of any single syndrome. Indicator variables for the comorbidities of the Charlson score [17] for most subjects were obtained in a report generated by Looking Glass that uses International Classfication of Diseases-9 codes from a 180-day period before the culture date to assign comorbidities to subjects [18]. For 5 subjects, the data for comorbidities were obtained by conventional review of the medical record, because the Charlson report was not available when those subjects were included in the study. Data for the other variables were abstracted from the chart by 1 of 4 reviewers. One study author (G.W.) audited a sampling of charts from the other reviewers to standardize the chart review.

Statistical Analysis

Univariate analyses for categorical variables used the Pearson chi-square test or the Fisher exact test as appropriate. Continuous variables were analyzed with the Mann-Whitney Wilcoxon rank-sum test. Statistical analyses were performed using STATA, version 13.1.

Variables with $P < .01$ on univariate analysis were included in an initial multiple logistic regression model with CRKP BSI as the outcome. To maintain a stable model, we kept the ratio of cases to variables at a minimum of 10:1. The P value .01 was chosen for initial model inclusion >.05 to maintain the 10:1 ratio. Variables with the highest P values were sequentially removed in a backwards elimination process until all remaining variables had P values <.05. Variables that had been removed

were then added back individually to confirm $P \geq .05$ and assess confounding. Confounding was defined as a change of >20% in the coefficient of a different variable in the model. Confounding variables were left in the model. First-order interactions were then assessed, and 1 interaction with the lowest P value <.05 was retained in the model. There was a highly significant interaction between the variables for mechanical ventilation and admission in the hospital for ≥3 days (72 hours). This finding was addressed by splitting the data set to develop 1 model for subjects with a positive blood culture in the first 3 days of admission and a different model for those with a positive blood culture at least 3 days after admission. Once the data set was split in these 2 groups with 2 models, variables that were no longer statistically significant were removed from 1 or both models. A sensitivity analysis using Firth's logistic regression derived the same models as standard logistic regression.

Model performance for each model was assessed with receiver operating characteristic (ROC) curves. The area under the ROC curve was determined with and without each variable in each model. Any variable that did not increase the area under ROC curve by at least .01 was removed. Estimated sensitivity and specificity of a classification rule using these 2 models in the data set were calculated using a 10-fold cross-validation analysis (see the Supplementary Appendix for detailed methods) [19]. The creation of a classification rule to discriminate subjects with relatively high probability of CRKP disease from those with lower probability requires choice of a cutoff point within the model. We calculated the estimated sensitivity, specificity, positive predictive value, and negative predictive value that would result from 2 different cutoff points.

RESULTS

The study team initially identified 187 potential cases and controls. Three potential cases were excluded because they had not received antibiotics within 48 hours of the blood culture, 20 potential cases were excluded because scanned medical records for those subjects were not available for review, and 1 potential case was excluded because of age <21, leaving a total of 163 cases. Nine potential controls were excluded for inability to review scanned medical records, leaving 178 controls.

Risk Factors for CRKP BSI From Univariate Analysis

Many variables were significantly associated with CRKP BSI in univariate analysis (Table 1). The variables with the strongest associations with CRKP BSI were prior nonblood culture with a CRE organism in the past 180 days, residence in an SNF before admission, mechanical ventilation in the past 30 days, and admission for at least 3 days at the time of blood culture. The variables most strongly associated with carbapenem-susceptible *Klebsiella* BSI were liver disease and suspected gastrointestinal source.

Table 1. Univariate Associations With CRKP Bloodstream Infection

Variable	Resistant *Klebsiella* (n = 163)	Susceptible *Klebsiella* (n = 178)	*P* Value
Age, y	69 (57–79)	68 (56–77)	.50[a]
Sex (male)	84 (52)	95 (53)	.73
Prior CRE culture[b]	60 (37)	6 (3.4)	<.001
No prior culture[b]	21 (13)	50 (28)	<.001
Admitted from SNF	99 (61)	42 (24)	<.001
Admitted >3 d	100 (61)	50 (28)	<.001
Last hospital discharge within 90 d	87 (53)	100 (56)	.61
Intensive care unit[c]	51 (31)	25 (14)	<.001
Mechanical ventilation[c]	90 (55)	36 (20)	<.001
Central line[c]	99 (61)	59 (33)	<.001
Indwelling urine catheter[c]	112 (69)	69 (39)	<.001
Endoscopy[c]	18 (11)	15 (8.4)	.41
Antibiotics[c]	128 (79)	78 (44)	<.001
Proton pump inhibitor[c]	110 (68)	81 (46)	<.001
Glucocorticoid[c]	52 (32)	39 (22)	.04
Congestive heart failure	41 (25)	36 (20)	.28
Chronic lung disease	45 (28)	47 (26)	.81
Liver disease	21 (13)	58 (33)	<.001
Diabetes mellitus	64 (39)	64 (36)	.53
Hemiplegia or paraplegia	16 (9.8)	7 (3.9)	.03
Malignancy	23 (14)	44 (25)	.01
Septic shock	53 (33)	34 (19.1)	.004
Urinary tract infection	51 (31)	57 (32)	.88
Pneumonia	42 (26)	30 (17)	.04
Gastrointestinal	16 (10)	53 (30)	<.001
Central line–associated	17 (10.4)	14 (7.9)	.41
Skin/soft tissue	10 (6.1)	5 (2.8)	.14
Central nervous system	1 (0.6)	0 (0)	.48[d]
Unknown	46 (28)	35 (20)	.06

Continuous variables are reported as median (interquartile range). Categorical variables are reported as number (percentage).

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; SNF, skilled nursing facility.

[a]Mann-Whitney test was used.

[b]Exposure occurred in the prior 180 days.

[c]Exposure occurred in the prior 30 days.

[d]Fisher exact test was used. Otherwise, for categorical variables, the Pearson χ^2 test was used.

Risk Factors for CRKP BSI From Multivariate Analysis

Multiple logistic regression derived an initial model including an interaction term and 8 variables (Table 2). Having a prior nonblood culture with a CRE organism, mechanical ventilation, admission for at least 3 days, and admission from an SNF remained strongly associated with CRKP BSI. Lack of any recorded culture in the prior 180 days and receipt of proton pump inhibitors in the prior 30 days were also associated with CRKP BSI. Liver disease was associated with carbapenem-susceptible *Klebsiella* BSI. Receipt of an antibiotic in the prior 30 days was included in this initial model due to a confounding effect on the variable admission of at least 3 days' duration. There was a statistically significant interaction between the variables mechanical ventilation and admission of at least 3 days' duration.

Table 2. Multivariate Models for CRKP Bloodstream Infection, Presented as Odds Ratios (95% Confidence Intervals)

Variable	Model With Interaction Term (n = 341)	Model for Patients Admitted <3 d (n = 191)	Model for Patients Admitted ≥3 d (n = 150)
Prior CRE culture[a]	16 (5.7–43)	16 (4.2–60)	15 (3.3–67)
Mechanical ventilation[b]	8.7 (2.9–26)	11 (3.5–37)	—
Admitted >3 d	4.6 (1.9–11)	—	—
Admission from SNF	4.5 (2.5–8.3)	3.7 (1.5–9.1)	5.5 (2.4–13)
No prior culture[a]	2.4 (1.0–5.5)	—	—
Proton pump inhibitor[b]	2.2 (1.1–4.2)	3.1 (1.2–7.6)	—
Antibiotics[b]	1.8 (0.8–3.9)	—	—
Liver disease	0.26 (0.12–0.57)	0.14 (0.042–0.43)	—
Admitted >3 d*mechanical ventilation interaction	0.12 (0.03–0.45)[c]	—	—
Constant	0.063 (0.027–0.14)	0.11 (0.049–0.24)	0.70 (0.43–1.1)

All variables in the models are shown.

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; SNF, skilled nursing facility.

[a]During the prior 180 days.

[b]During the prior 30 days.

[c]$P_{interaction}$ = .001.

There were 128 controls and 63 cases in the group of subjects with a *Klebsiella* BSI in the first 3 days of admission. In these subjects, the variables prior CRE culture, mechanical ventilation, admission from a skilled nursing facility, receipt of a proton pump inhibitor, and comorbidity of liver disease were statistically significant. Each of these variables made an acceptable contribution to the area under the ROC curve and was retained in the model for this group of subjects (Table 2). The area under the ROC curve for this model was 0.88. There were 50 controls and 100 cases in the group of subjects with *Klebsiella* BSI at or beyond 3 days of admission. In this group, the variables prior CRE culture and admission from a skilled nursing facility were statistically significant. Each contributed to the area under the ROC curve and was retained in the model for this group of subjects (Table 2). The area under the ROC curve for this model was 0.78.

The multivariate models are shown in Table 3 with regression coefficients and constants. We examined 2 ways to use the models to classify subjects as having high or low probability of CRKP disease. A less sensitive but more specific classification rule would classify as high probability of CRKP disease any subject for whom the sum of the regression coefficients of the variables that are true is greater than the absolute value of the regression constant. For subjects with a *Klebsiella* blood culture in the first 3 days of admission, the sum of the regression coefficients would have to be >2.2 to classify the patient in the high probability group (Figure 1). For subjects with a *Klebsiella* blood culture at least 3 days after admission, the presence of a prior CRE culture or admission from a skilled nursing facility would classify the patient in the high probability group. A more sensitive but less specific classification rule would classify all subjects with a *Klebsiella* blood culture at least 3 days after admission in the high probability group while making no change to the classification for subjects with a *Klebsiella* blood culture in the first 3 days of admission (Figure 1).

Cross-validation analysis estimated that the derived models for CRKP BSI could give reasonable guidance in identifying patients with high probability of CRKP BSI. Such patients would be candidates for empiric anti-CRKP therapy in clinical practice (algorithmic use of the models shown in Figure 1). The median estimated sensitivity and specificity for the less sensitive classification rule were 72% and 88%. The median estimated sensitivity and specificity for the more sensitive classification rule were 87% and 69%. For every patient appropriately given empiric anti-CRKP therapy, we estimate that the number of patients with susceptible *Klebsiella* who receive unnecessary anti-CRKP therapy would be 0.7 for the less sensitive classification rule and 1.7 for the more sensitive classification rule (Table 4).

Table 3. Multivariate Models for CRKP Bloodstream Infection, Presented as Regression Coefficients

Variable	Model for Patients Admitted <3 d (n = 191)	Model for Patients Admitted ≥3 d (n = 150)
Prior CRE culture[a]	2.8	2.7
Mechanical ventilation[b]	2.4	—
Admission from SNF	1.3	1.7
Proton pump inhibitor[b]	1.1	—
Liver disease	–2.0	—
Constant	–2.2	–0.36

All variables in the model are shown.

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; SNF, skilled nursing facility.

[a]During the prior 180 days.

[b]During the prior 30 days.

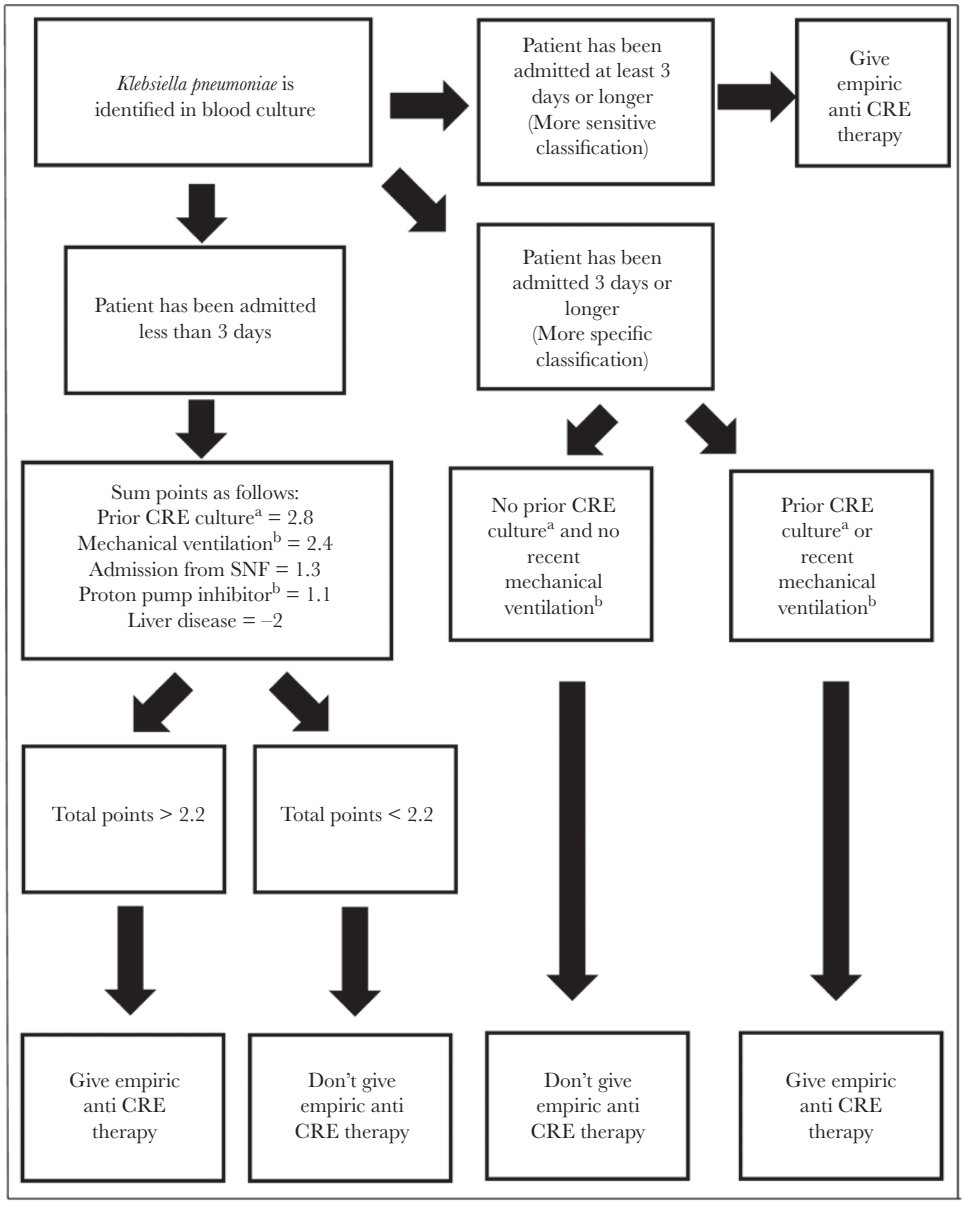

Figure 1. Flow sheet for clinical classification rules for CRKP bloodstream infection to guide empiric antibiotic therapy. [a]During the prior 180 days. [b]During the prior 30 days. Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella* pneumoniae.

DISCUSSION

The high mortality associated with CRKP BSI and the delay in providing appropriate antibiotic therapy underscore a need to identify patients with CRKP BSI earlier in the disease course. Kohler et al. found that a lack of appropriate initial therapy is associated with increased odds of death in CRKP BSI compared with CSKP BSI [20]. The models derived here have the potential to guide clinicians at our medical center to initiate appropriate antibiotic therapy earlier for patients with CRKP BSI.

History of a nonblood culture with a CRE organism in the prior 180 days was a strongly associated factor. We cannot comment on the strength of the association for prior CRE-positive blood cultures because our case patients were studied at the time of first CRKP BSI. Association of prior nonblood culture results with the CRKP BSI outcome does not prove that colonization with CRE organisms leads to disease, but it does support the value of reviewing a patient's prior culture results when choosing therapy for acute infections. It also suggests that coordination among regional facilities to share colonization or infection data could be useful in therapeutic and infection control decisions [21]. The strong association of admission from a skilled nursing facility with CRKP BSI underscores the need to

Table 4. Clinical Utility of 2 Classification Rules for CRKP BSI

Classification Rule	Estimated Sensitivity, %	Estimated Specificity, %	Estimated Positive Predictive Value, %	Estimated Negative Predictive Value, %	Estimated False-Positive to True-Positive Ratio
Less sensitive	72	88	58	93	0.73
More specific	(65–75)	(84–92)	(52–64)	(92–94)	(0.57–0.94)
More sensitive	87	69	37	96	1.7
Less specific	(83–90)	(56–71)	(34–41)	(94–97)	(1.4–1.9)

Estimated performance of the CRKP BSI score in a population with prevalence of CRKP BSI equal to that found in our cohort (prevalence 18%). Results are reported as median (interquartile range).

Abbreviations: BSI, bloodstream infection; CRKP, carbapenem-resistant *Klebsiella* pneumoniae.

include long-term care facilities in regional cooperative infection control and antibiotic stewardship efforts.

This study presents 2 classification rules for determining which patients should receive anti-CRKP therapy. The more sensitive classification rule presented here would capture more patients that have CRKP disease than the less sensitive rule at the cost of exposing more than twice as many patients to unnecessary anti-CRKP therapy. The dangers of exposing more patients to anti-CRKP therapy include risk of antibiotic side effects and more rapid development of resistance to new antimicrobial agents. There is a trade-off between giving early active therapy for more patients with CRKP disease and avoiding unnecessary anti-CRKP therapy for patients who do not have carbapenem-resistant infections. Research to determine the optimal balance for these goals of therapy is needed.

Previous studies have identified risk factors for CRKP colonization and disease. Admission from an SNF and exposure to mechanical ventilation have been associated with CRKP rectal colonization [8, 9, 11]. Our study focused on CRKP BSI specifically. Studies by Richter et al. and Lodise et al. developed clinical prediction tools for carbapenem-resistant gram-negative organisms [22, 23]. These studies differ from the work described here because they study multiple species of bacteria. The significant risk factors reported in these studies may be associated with a species such as *Klebsiella* that is more likely to be carbapenem resistant and may not be associated with carbapenem resistance itself. Furthermore, these tools derived using multiple culture sources in the outcome and using administrative databases may predict nondisease colonization in addition to disease with carbapenem-resistant bacteria. The clinical prediction tools proposed by Richter and Lodise are applicable at the point of care when a clinician does not know the species infecting the patient. The clinical tool reported here is applicable at a different point in care—when the clinician knows that a patient has *Klebsiella* BSI without susceptibility information. Leibman et al. developed a bedside score to guide therapy for CRE [24]. Leibman et al. found recent chemotherapy to be the strongest risk factor and did not include SNF residence in their model. Our study found that SNF residence was an important risk factor but that recent chemotherapy was not. This may result from differences in the epidemiology of carbapenem resistance in the study populations. It may be appropriate to use different models to guide empiric therapy in different populations. Another difference in the model derived by Leibman et al. is that CRE BSI was compared with BSI with extended-spectrum beta-lactamase (ESBL) organisms. This model would be clinically useful in situations when a provider knows she is treating either an ESBL or CRE organism. The models derived in our study provide information for a more common scenario in our institution—*Klebsiella* BSI awaiting susceptibility determination. This scenario occurs routinely with the use of MALDI-TOF technology. Different models for carbapenem-resistant gram-negative infections may be applicable in different situations and should be used only when applicable.

There are several limitations to this study. First, it is retrospective and could have unmeasured confounding. Second, CRKP BSI was not evenly distributed among the hospitals in our study, so the hospital location may have had a confounding effect. Third, the 3 hospitals in this study are from the same hospital system and care for patients from similar demographic areas. These results may not be generalizable to other locations. Furthermore, analysis of the clinical utility of the models depends on the prevalence of CRKP BSI in the population and is not applicable in areas where CRE is not endemic. Fourth, although we measured the presence of prior clinical nonblood cultures with CRE organisms, we only had access to data within the Montefiore hospital system, and we had no data on CRE rectal colonization. The proportion of subjects with prior colonization or prior infection with CRE organisms may have been underestimated. A similar limitation is present for other variables such as exposure to antibiotics or exposure to medical devices in other institutions. Fifth, some medical records were unavailable because they were never scanned into our electronic system. Unavailability of medical records was most prevalent in the case group. Subjects with CRKP BSI may have been more likely to have long paper charts that were cumbersome to scan. This may have led to underestimation of the prevalence of health care exposures in the CRKP BSI group, which would have biased the results toward the null and could have affected the accuracy of the strength of association estimates. Finally, our study describes the derivation of a clinical classification tool but does not test the tool in a validation cohort. In

the future, we plan to evaluate both the more sensitive and less sensitive classification rules in a validation cohort.

This study also has important strengths. First, it is the largest risk factor study of CRKP BSI known to us. Unlike urine, lung, or wound infections, in BSI there is no doubt of the clinical relevance of the infection. Second, review of the charts allowed study of potential risk factors, such as suspected source of infection, that are difficult to study via electronic chart abstraction. Third, the study was designed to identify risk factors for CRKP BSI at a clinical decision point, the time of species identification without organism susceptibilities, which could have directed antibiotic choice. Fourth, the study was built in a high–CRE prevalence area that has the greatest need for guidance in treating CRE infections. This study presents a clinical tool that can be further evaluated for use in our own medical center as well as others. Even if the specific model needs modification in different hospitals, the approach we have described can be used at other institutions to develop appropriate local therapeutic strategies.

This study found that a classification rule to guide empiric therapy against CRKP at the time of identification of *Klebsiella* in blood culture has potential clinical utility and requires further study. Clinicians in areas of CRE endemicity can evaluate this model for use in their own medical centers, but may need to study the local epidemiology of resistance to optimally guide therapy in their own populations.

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