American Journal of Infection Control 42 (2014) 612-20

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Outcomes of carbapenem-resistant *Enterobacteriaceae* isolation: Matched analysis

Christopher Bogan BS [a], Keith S. Kaye MD, MPH [a], Teena Chopra MD, MPH [a], Kayoko Hayakawa MD, PhD [a], Jason M. Pogue PharmD [b], Paul R. Lephart PhD [c], Suchitha Bheemreddy MD [a], Tsilia Lazarovitch PhD [d], Ronit Zaidenstein MD [e], Federico Perez MD [f,g], Robert A. Bonomo MD [f,g,h,i,j], Dror Marchaim MD [e,k,*]

[a] *Department of Medicine, Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Detroit, MI*
[b] *Department of Pharmacy Services, Detroit Medical Center, Wayne State University, Detroit, MI*
[c] *Department of Clinical Microbiology, Detroit Medical Center, Wayne State University, Detroit, MI*
[d] *Department of Clinical Microbiology, Assaf Harofeh Medical Center, Zerifin, Israel*
[e] *Division of Infectious Diseases, Assaf Harofeh Medical Center, Zerifin, Israel*
[f] *VISN 10 Geriatric Research, Education, and Clinical Centers (GRECC) at Veterans Affairs Medical Center, Cleveland, OH*
[g] *Department of Medicine, Veterans Affairs Medical Center, Cleveland, OH*
[h] *Research Service, Veterans Affairs Medical Center, Cleveland, OH*
[i] *Department of Pharmacology, Case Western Reserve University, Cleveland, OH*
[j] *Department of Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, OH*
[k] *Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

Key Words:
CRE
KPC
Outcome
Cohort study
Case control
Risk factors

Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) isolation is associated with poor outcomes. The matched cohort study design enables investigation of specific role of resistance in contributing to patients' outcomes. Patients with CRE were matched to 3 groups: (1) patients with extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL), (2) patients with carbapenem-susceptible non-ESBL *Enterobacteriaceae*, and (3) uninfected controls.

Methods: Patients with CRE isolated at Detroit Medical Center (September 1, 2008, to August 31, 2009) were matched (1:1 ratio) to the 3 groups based on (1) bacteria type, (2) hospital/facility, (3) unit/clinic, (4) calendar year, and (5) time at risk (ie, from admission to culture). Multivariable logistic regression models for outcomes were constructed.

Results: Ninety-one patients with CRE were enrolled. CRE isolation was not an independent predictor for in-hospital mortality in any of the models (ie, vs uncolonized controls, vs ESBL, vs non-ESBL *Enterobacteriaceae*, and vs all 3 non-CRE groups combined), despite high significance of association in bivariate analyses. CRE isolation was independently associated with deterioration in functional status [odds ratio, 9; $P = .002$] and being discharged to a long-term care facility after being admitted to the hospital from home [odds ratio, 13.7; $P < .001$].

Conclusion: Underlying condition and comorbidities are the principal factors responsible for in-hospital mortality in CRE infections; however, in-hospital mortality is not independently correlated to the offending pathogen. In addition, we found that the pathogen contributes significantly to patients' degree of morbidity.

* Address correspondence to Dror Marchaim, MD, Division of Infectious Diseases, Assaf Harofeh Medical Center, Zerifin, 70300, Israel.
E-mail address: drormc@hotmail.com (D. Marchaim).

Supported by the National Institute of Allergy and Infectious Diseases (NIAID), DMID protocol number: 10-0065 (to K.S.K.); by the VISN 10 Geriatric Research, Education, and Clinical Centers (GRECC; to F.P.) at the Veterans Affairs Medical Center and the Cleveland Translational Science Award (UL1TR000439; to F.P.); and National Institutes of Health award numbers R01AI072219, R01AI063517, and R01AI100560 (to R.A.B.) and by funds and/or facilities provided by the Louis Stokes Cleveland Department of Veterans Affairs Medical Center and the VISN 10 Geriatric Research, Education and Clinical Care Center (VISN 10) of the Department of Veterans Affairs (to R.A.B.).

Funding organizations were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Veterans Administration.

Conflicts of interest: None to report.

http://dx.doi.org/10.1016/j.ajic.2014.02.013

Antimicrobial resistance, particularly among gram-negative bacteria, pose a significant public health threat and economic burden because effective therapeutics are sorely lacking.[1-6] Among gram-negative bacteria that are most problematic, carbapenem-resistant *Enterobacteriaceae* (CRE) merit significant attention. The emergence of resistance to carbapenems among common enteric bacteria is perceived as a "sentinel event" in the medical community.[4] Several institutions, regions, and even some countries have issued specific measures to try and contain the spread of CRE.[7,8] Despite these measures, the epidemiology of CRE continues to evolve as these pathogens rapidly disseminate worldwide causing numerous outbreaks.[8-17]

In analyses conducted thus far, CRE isolation is associated with significantly increased mortality, length of hospital stay (LOS), and costs.[18-24] Frequently, delays in initiation of appropriate antimicrobial therapy among CRE carriers are also reported.[23,25] Regrettably, delayed diagnosis of CRE is often because of multiple factors: (1) the low sensitivity of routine automated screening methods,[7] (2) slow microbiologic processing of cultures when using conventional methods,[26] and (3) lack of awareness and recognition of CRE by clinicians and laboratory personnel. The lack of effective therapeutic options (especially for panresistant isolates) adds to this predicament.[27,28]

Delay in initiation of appropriate antimicrobial therapy is the strongest modifiable predictor for mortality in severe sepsis,[29] but many previous CRE outcomes analyses have not captured the impact of this and/or properly controlled for it.[19,21,24] Worse outcomes were observed among CRE carriers, but it is not clear how delays in initiating appropriate therapy, the pathogen (with regards to its virulence properties), and the host (eg, age, comorbidities, and others) contribute each to these unfavorable outcomes. Understanding the role of delay in initiating appropriate therapy compared with the intrinsic properties of the pathogen (eg, virulence) or of the patient—in contributing to inferior outcomes among patients—is an important goal; one must have clear insights into these factors to properly allocate preventive resources (both fiscal and temporal).

Reference group selection plays a critical role in determining which predictors are identified in case-control studies pertaining to antimicrobial-resistant organisms.[30-32] The case-case-control study design is a standard approach for accurately studying the unique epidemiology associated with isolation of antimicrobial-resistant pathogens.[31] This study design is used primarily for risk factors analyses.[18,33] However, case-case-control studies are also effective in eliminating possible confounders while studying the specific role of a resistance determinant on patients' clinical outcomes.[18,34]

Several of the previous CRE outcomes analyses considered patients with carbapenem-susceptible *Enterobacteriaceae* as controls, without using a group of patients who did not have *Enterobacteriaceae* isolated ("uncolonized controls"). Other analyses did not appropriately match uncolonized controls to cases.[35,36] Some studies employed a case-case-control study design, but the carbapenem-susceptible *Enterobacteriaceae* group included both extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL) as well as non-ESBL containing *Enterobacteriaceae*.[18] Such a design raises questions because ESBL production contributes independently to adverse clinical outcomes, thus making the carbapenem-susceptible reference group heterogeneous in terms of outcomes risk.[37] We propose to use a matched cohort analysis of outcomes, which utilizes similar "control groups" as the case-case-control study design, but is primarily used to determine the impact of antimicrobial-resistant pathogens and determinants on clinical outcomes. Study aim therefore was to investigate outcomes of patients with CRE isolation (both infected and colonized-only individuals) throughout the continuum of medical care (including long-term care facilities [LTCFs] and outpatient clinics), using matched outcomes analyses and including 3 reference groups: (1) patients with carbapenem-susceptible ESBL-producing *Enterobaceriaceae*; (2) patients with carbapenem-susceptible, non-ESBL-producing *Enterobacteriaceae*; and (3) patients without isolation of *Enterobacteriaceae* (ie, uncolonized controls).

METHODS

Study settings and design

The Detroit Medical Center (DMC) health care system consists of 8 hospitals, more than 2,200 inpatient beds, and serves as a tertiary referral facility for metropolitan Detroit and southeastern Michigan. DMC has a single centralized Clinical Microbiology Laboratory (DMC-CML), which processes ~ 500,000 samples per annum. Multiple outpatient facilities in southeast Michigan use these laboratory services on a routine basis. Patient charts, pharmacy records, and microbiologic data are all stored and managed electronically at DMC.

CRE was defined as any *Enterobacteriaceae* isolate that was either resistant to any carbapenem based on established Clinical and Laboratory Standards Institute (CLSI) breakpoints at the time of the study[38] or determined to be a carbapenemase producer per phenotypic (Modified Hodge Test) or genotypic (bla_{KPC} polymerase chain reaction) test.[39] Institutional review boards at Wayne State University, Cleveland Veterans Affairs Medical Center, and DMC approved the study before its initiation.

Patients possessing CRE that were isolated from September 1, 2008, to August 31, 2009, were matched in 1:1 ratio to patients in 3 different reference groups: (1) patients with ESBL-producing *Enterobacteriaceae*, (2) patients with susceptible non-ESBL-producing *Enterobacteriaceae*, and (3) uncolonized control patients who did not have *Enterobacteriaceae* isolated. Matching parameters included the following: the *Enterobacteriaceae* species (for groups 1 and 2), hospital or outpatient facility, unit or clinic, calendar year, and time at risk (ie, time from admission to culture for patients with *Enterobacteriaceae*). For uncolonized controls, the total duration of hospital stay was the time at risk and had to be at least as long as the time at risk of the case to which they were matched. If multiple patients met matching criteria, a subject was randomly selected using the randomization function in Excel (Microsoft Corp, Redmond, WA).

Patients and clinical variables

CRE cases consisted of all patients who had a CRE (as per aforementioned definition) recovered from a clinical sample sent from inpatient and outpatient facilities that submit specimens to DMC-CML. Active surveillance screening cultures were not performed routinely during the study period and were excluded from the analysis. Cultures from all anatomic sites were collected, and both infected and colonized patients were included. Infections were defined according to Centers for Disease Control and Prevention criteria and the presence of systemic inflammatory response syndrome.[40,41] For patients who had more than 1 CRE isolate during the study period, only the first episode of CRE isolation was analyzed.

Epidemiologic parameters retrieved from electronic records included the following: (1) demographics, (2) background and comorbid conditions, (3) recent health care-associated exposures including invasive procedures and devices, (4) acute severity of illness indices, (5) exposures to antimicrobials in the 3 months prior to culture or admission (for uncolonized controls), (6) time to initiation of appropriate antimicrobial therapy, and (7) empiric