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## Emergence of carbapenem-resistant *Enterobacteriaceae* in Orange County, California, and support for early regional strategies to limit spread

Shruti K. Gohil, MD, MPH<sup>a,\*</sup>, Raveena Singh, MA<sup>a</sup>, Justin Chang<sup>a</sup>, Adrijana Gombosov, MS<sup>a</sup>, Tom Tjoa, MPH, MS<sup>a</sup>, Matthew Zahn, MD<sup>b</sup>, Patti Steger, CLS, MT(ASCP), CIC<sup>c</sup>, and Susan S. Huang, MD, MPH<sup>a</sup>

<sup>a</sup>Division of Infectious Diseases and Health Policy Research Institute, University of California Irvine School of Medicine, Irvine, CA

<sup>b</sup>Orange County Health Care Agency, Santa Ana, CA

<sup>c</sup>Association for Professionals in Infection Control and Epidemiology, Chapter 029 Orange County, Orange, CA

### Abstract

**Background:** The east-to-west spread of carbapenem-resistant *Enterobacteriaceae* (CRE) represents an opportunity to explore strategies to limit spread in nonendemic areas. We evaluated CRE emergence and regional support for containment strategies.

**Methods:** A 17-question cross-sectional survey was administered to infection prevention programs in Orange County, CA (31 hospitals serving 3 million residents), between January and September 2014. Questions addressed newly detected hospital- and community-onset CRE cultures (2008-2013), current CRE control strategies, and support for prevention strategies for a hypothetical regional intervention.

**Results:** Among 31 hospitals, 21 (68%, representing 17 infection prevention programs) completed the survey. CRE was scarcely detected between 2009-2010; within 4 years, 90% of hospitals reported CRE, with 2.5-fold higher community-onset than hospital-onset CRE. Between 2011 and 2013, annual CRE incidence increased 4.7-fold (1.4-6.3 cases/10,000 admissions). Support for a regional CRE prevention bundle was unanimous. Although 22% bathed patients positive for CRE with chlorhexidine gluconate and 11% actively screened for CRE, 86% and 57%, respectively, would consider these strategies in a regional intervention.

\* Address correspondence to Shruti K. Gohil, MD, MPH, Division of Infectious Diseases, University of California Irvine Medical Center, 333 City Blvd, W, Ste 400, Orange, CA. skgohil@uci.edu.

#### SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ajic.2017.06.004>.

Preliminary findings from this work were presented at the Infectious Disease Society of America Annual Meeting, October, 2014, Philadelphia, PA.

Conflicts of interest: SG has served as coinvestigator for studies in which participating facilities may have received contributed product from Clorox. SSH, AG, and RS have conducted clinical studies for which participating hospitals and nursing homes have received contributed product from Sage Products, Molnlycke, 3M, and Clorox.

**Conclusions:** CRE epidemiology in Orange County parallels early progression previously seen in now-endemic areas, representing an opportunity to consider interventions to prevent endemic spread. Many facilities would consider proactive strategies, such as chlorhexidine bathing, in the setting of a regional collaborative.

### Keywords

Emerging infections; Antibiotic resistance; Infection prevention of multidrug-resistant organisms

The global rise of carbapenem-resistant *Enterobacteriaceae* (CRE) over the past decade marks an important opportunity to consider the role of aggressive and proactive infection prevention efforts in the fight against multidrug-resistant organisms (MDROs).<sup>1-5</sup> Amongst MDROs, CRE is among the deadliest, with mortality of infection reported to range from 30%-50%.<sup>6-12</sup> Mobile genetic elements associated with CRE resistance mechanisms exacerbate the risks of transmission associated with CRE carriage, with epidemiologic evidence of rapid spread in prior outbreaks.<sup>7,13</sup> In the context of extremely limited therapeutic options, CRE represents a high-risk MDRO for which primary prevention strategies to limit CRE spread could prove critical.<sup>4,5,7,14</sup>

When applied across communities, aggressive and proactive infection prevention interventions can mitigate both acquisition and transmission risk and significantly influence CRE spread.<sup>5,15,16</sup> Most notably, a national infection prevention intervention in Israel successfully decreased the monthly incidence of hospital-onset CRE by nearly 80% using interventions such as aggressive hand hygiene compliance, contact precautions, patient cohorting, and active surveillance screening.<sup>4,5</sup> To date, hospital and regional interventions have only occurred in the setting of CRE outbreaks. However, the greatest potential for influence of regional horizontal strategies in infection prevention is at the earliest opportunity, before widespread dissemination occurs.<sup>15,17</sup>

In this study, we describe the emergence of CRE in Orange County, CA, the sixth largest county in the United States, and assess the current infection prevention strategies employed by acute care facilities specifically against CRE. Although facility and regional level interventions are most often considered in the setting of an outbreak, it is unclear how such interventions would be supported before MDRO spread reaches endemic proportions within a community. We therefore assessed the level of support for a hypothetical regional CRE collaborative involving primary prevention strategies to limit CRE spread in hospital settings.

## METHODS

### Data collection and survey design

We administered a survey consisting of 14 questions and 3 data tables (Appendix S1) to the infection prevention and control (IPC) programs of 31 hospitals in Orange County, CA, between January and December 2014. This survey was approved by the University of California Irvine Institutional Review Board. Participation was voluntary and facilities were recruited with the help of the Orange County chapter of the Association for Professionals in

Infection Control and Epidemiology. Descriptive data characterizing participating hospital metrics such as hospital admissions, length of stay, patient demographic characteristics, and case mix were obtained from a mandatory state hospitalization data set.<sup>18</sup> The survey was completed either on paper or online through SurveyMonkey ([www.surveymonkey.com](http://www.surveymonkey.com)), per hospital preference. Any surveys with incomplete information were followed-up with a telephone call and in-person meeting with hospital IPC programs to encourage completion. Participants were asked to complete data tables reporting aggregated facility-level hospital-onset (HO) and community-onset (CO) CRE cases per year from 2008-2013. Incident cases were defined based on clinical cultures, which represented newly detected (ie, first-known positive CRE for that patient in that hospital) and were designated as HO (>2 days after admission) or CO (≤ 2 days) by dates. CRE were defined according to each facilities' laboratory definitions (see Results). Incident CRE cases were confirmed with microbiologic laboratory reports. CRE cases were designated as CO if date of culture positivity was ≤ 2 days after admission and otherwise as HO.

The survey additionally included a series of questions to assess CRE surveillance definition, strategies in place to address CRE, and support for countywide regional CRE collaborative strategies. The latter 2 were aimed at evaluating current practice and the level of support for IPC strategies to limit intra- and interfacility CRE spread. These strategies included contact precautions for patients with CRE infection, cohort nursing, interfacility communication of patients admitted from or discharged to other facilities, rectal screening for high-risk patients (ie, patients with indwelling devices, from nursing home or long-term acute care facilities, or patients in same or neighboring rooms of patients with known CRE infection), 1-day point prevalence screens, and daily bathing with chlorhexidine gluconate (CHG). For support for a regional response, respondents were asked to rate their willingness to support each strategy above on 5-point Likert scale ranging from “definitely will support” to “definitely will not support.” Survey items are provided in Appendix S1.

### Data analysis

Descriptive proportions were calculated using the total number of hospitals responding to each survey item as the denominator. When assessing support for regional strategies for CRE prevention, respondents were designated as “supportive” if they chose either “definitely will support” or “possibly will support” responses. CRE incidence was reported as the number of new hospital or community onset cases per 1,000 annual admissions.

## RESULTS

Among 31 hospitals, 17 infection prevention programs responded, representing 21 hospitals (response rate, 68%). Table 1 shows the characteristics and case mix of participating hospitals in 2013. Together, they represented 212,047 annual admissions and 931,216 annual patient days; characteristics were similar to statewide demographic characteristics of hospital admissions.<sup>18</sup> Few cases of CRE were seen in Orange County between 2009 and 2010, with only 24% of hospitals reporting CRE cases. By the end of the study period, CRE had been detected in 90% of hospitals. Between 2011 and 2013, the annual incidence of CRE cases rose 4.7-fold, from 1.4-6.3 cases/10,000 admissions representing an absolute

number of CRE cases increase from 72-253 within 2 years (Fig 1A). Much of this rise was concentrated within only 5 (24%) facilities reporting 20 or more cases and accounting for 198 (78%) of all cases by 2013 despite representing only 29% of all patient days in participating hospitals that year (Fig 1B). Among these 4 facilities, 1 was an academic tertiary care medical center and the remaining 3 were community hospitals. Aside from 1 hospital, most CRE cases in the county were CO (Fig 1C), although respondents commented that HO cases may have been misclassified because detection was commonly noted in transfers from nursing homes. Among CRE isolates, all were clinical cultures except 2 that were screening cultures only; 69.7% were *Klebsiella* species (97% of which were *Klebsiella pneumoniae*), 16.9% were *Escherichia coli*, and 13.4% were *Enterobacter* species.

At the time of survey, 82% (14 out of 17) of infection prevention programs defined CRE as intermediate or full resistance to any carbapenem; 12% (2 out of 17) defined CRE as intermediate or full resistance to all carbapenems except ertapenem and 1 program did not respond. Infection prevention strategies in place for CRE at the time of survey are shown in Table 2. All facilities were using contact precautions (gowns and gloves) and single-room isolation and had a process in place to track CRE, with 14 (67%) having an electronic medical record flag in place. The majority reported some form of communication to other facilities regarding CRE status. Few hospitals (11%) had instituted active screening for high-risk or CRE-exposed patients. One hospital screened patients in neighboring rooms of patients found to have HO CRE. One facility screens all admitted patients received from nursing homes or other acute care hospitals.

Table 3 shows how many hospitals would support pursuing specific infection prevention strategies in a hypothetical regional CRE collaborative. Support for contact precautions and interfacility communication was unanimous. Although more resource-intensive interventions such as biannual prevalence screening or screening of high-risk incoming patients were less well-supported, more facilities were willing to consider these interventions in the setting of a hypothetical collaborative compared with current practices.

CHG bathing for adult inpatients (regardless of MDRO status) had been implemented in at least 1 intensive care unit at 65% (11 of 17 respondents) of facilities at the time of survey, the remainder did not use CHG bathing as an infection prevention strategy for any inpatient. One facility bathed patients housewide, regardless of MDRO status. CHG bathing of known CRE carriers was widely supported (86% of facilities) for a hypothetical CRE prevention bundle.

## CONCLUSIONS

The emergence of CRE in Orange County, CA, during late 2009 to early 2010 has been accompanied by a precipitous rise in prevalence, from 1.4-6.3 cases per 10,000 admissions between 2011 and 2013. This parallels early epidemiology seen in other areas where CRE is now endemic.<sup>2,3,19,20</sup> Although CRE has emerged in our county, it is not yet endemic, representing an important opportunity to consider regional approaches to curb further spread.

CRE incidence increased rapidly in our county despite the fact that all facilities surveyed reported instituting prompt contact precautions and providing interfacility communication, suggesting that such efforts to contain CRE within facilities are insufficient to influence regional spread. This may be due to the fact that clinical cultures only identify a small fraction of CRE carriers and because interfacility communication only occurs during direct transfers, which represent only 6% of patient-sharing events among hospitals in this county.<sup>21</sup>

CRE was detected in 90% of responding hospitals, with CO cases outnumbering HO cases 2.5-fold. It is unclear whether HO cases may represent delayed identification of imported cases either due to delayed culturing or unmasking of CRE due to selective pressure by treatment antibiotic agents. In addition, we were not able to distinguish CO CRE cases from Healthcare Associated Community Onset cases due to lack of information on whether these individuals were recently hospitalized or in nursing homes just before their admission to the reporting hospital. We recognize that CRE has been reported to be more commonly found in long-term care settings compared with hospitals.<sup>1,3,22</sup> The disproportionately high number of imported CRE cases highlights the importance of pursuing a regional collaborative approach to minimize CRE spread across hospitals, skilled nursing facilities, and long-term acute care facilities.

The Centers for Disease Control and Prevention (CDC) estimates that infection prevention and antibiotic stewardship interventions occurring at a national level could prevent 619,000 health care-associated infections due to MDROs over 5 years.<sup>23</sup> Lee et al<sup>24</sup> modeled the differential influence of the CDC CRE prevention toolkit when adopted at the facility level only versus a coordinated regional effort and found that a regional effort would result in an additional 21% reduction in CRE prevalence. Regional strategies to interrupt acquisition and transmission as early as possible among shared patients represents a unique opportunity to prevent endemic MDRO prevalence. In response to international and national outbreaks of CRE, the CDC issued guidance that promoted implementation of a series of core strategies at both facility and regional levels during 2012.<sup>2,3,5,16,17</sup> Adoption of such strategies in areas where CRE is not yet endemic is unknown. Although primary prevention strategies are less commonly used in infection prevention when prevalence is rare or low, pre-emptive action taken before spread could serve a critical role in preventing this pathogen from gaining a foothold in a region.

In this study, we sought to contrast infection prevention practices currently in place with support for practices if they were part of a regional collaborative within the context of a newly emerging MDRO. Aside from contact precautions that would be implemented for any MDRO, we found that few facilities had implemented proactive strategies such as active screening protocols for early identification of CRE carriers or exposed patients. This level of response is not surprising in a community where CRE levels are low. Importantly, support for such strategies was higher in the context of a hypothetical regional collaborative, implying that public health initiatives have the potential to influence additional actions. Although this survey did not assess attitudes and beliefs, a possible reason for higher support in the setting of a regional collaboration may include acknowledgment of the importance of

such strategies for the communities they serve, or recognition that early proactive efforts may result in future gains for their hospitals.

Infection prevention programs were very willing to perform targeted periodic monitoring of hand hygiene and contact precautions for rooms housing CRE carriers. Broad support for this strategy is not surprising given hand hygiene and contact precautions compliance monitoring is well embedded within activities at most infection prevention programs. In addition, we found that daily CHG bathing of known CRE carriers was among the best supported active interventions among hospitals for a regional collaborative to prevent CRE. Body surface decolonization with daily CHG bathing has been shown to reduce the risk of acquisition and transmission of MDROs and the risk for health care-associated infections, including surgical site infections and central line-associated bloodstream infections.<sup>25-31</sup> Daily CHG has also been shown to reduce the risk of CRE acquisition and transmission and several other studies have demonstrated its effectiveness in preventing HAIs from gram negative pathogen.<sup>4,26,32-35</sup> Favorability of this intervention may have stemmed from the fact that the majority of hospitals had already introduced CHG bathing into at least 1 hospital intensive care unit. The high willingness to adopt either periodic compliance monitoring or CHG bathing was likely also due to the targeted nature of these strategies, which would currently need to be applied to very few patients.

Among all proposed regional collaborative intervention strategies, active screening received the most mixed support. These findings are not unexpected in light of the high cost and resource-intensive nature of surveillance screening and the unclear role of screening cultures in guiding infection prevention strategies, particularly when prevalence is low. Given the body of literature supporting early identification of CRE and prompt prevention responses resulting in significantly decreased risk of acquisition and transmission where CRE is endemic, further studies are needed to address the role of screening strategies and their cost-effectiveness in early prevention efforts.<sup>4,5,16,36</sup>

Our study has several limitations. Current strategies and practices for CRE prevention were assessed by facility report without concomitant assessment of compliance. Second, we were unable to identify the exact source or time of CRE acquisition, making any assignment of HO or CO limited due to lack of complete knowledge of recent exposures to a health care facility. Third, this survey period encompassed a time when CRE definitions had been revised twice; thus, responding facilities were likely in varying phases of adopting guidance.<sup>37</sup>

Contact precautions and interfacility communication remain the most common responses to CRE despite mounting media and literature documenting outbreaks and the rise of CRE to endemic proportions in other areas of the country. The arrival of CRE in Orange County, CA, was anticipated as CRE traversed the United States from east to west. Upon arrival, our study describes a rapid increase in numbers. We found that many facilities are willing to consider more proactive infection prevention strategies, such as hand hygiene and contact precaution monitoring and targeted CHG bathing, in the setting of a regional collaborative to limit CRE spread. A sizeable minority were willing to perform some form of targeted screening of roommates or transfers from high-risk facilities, and this fraction may increase

as incidence rises in a region. Investment in public health initiatives may be critically important for motivating hospitals and engendering organized efforts to prevent emerging diseases from gaining a foothold in nonendemic areas.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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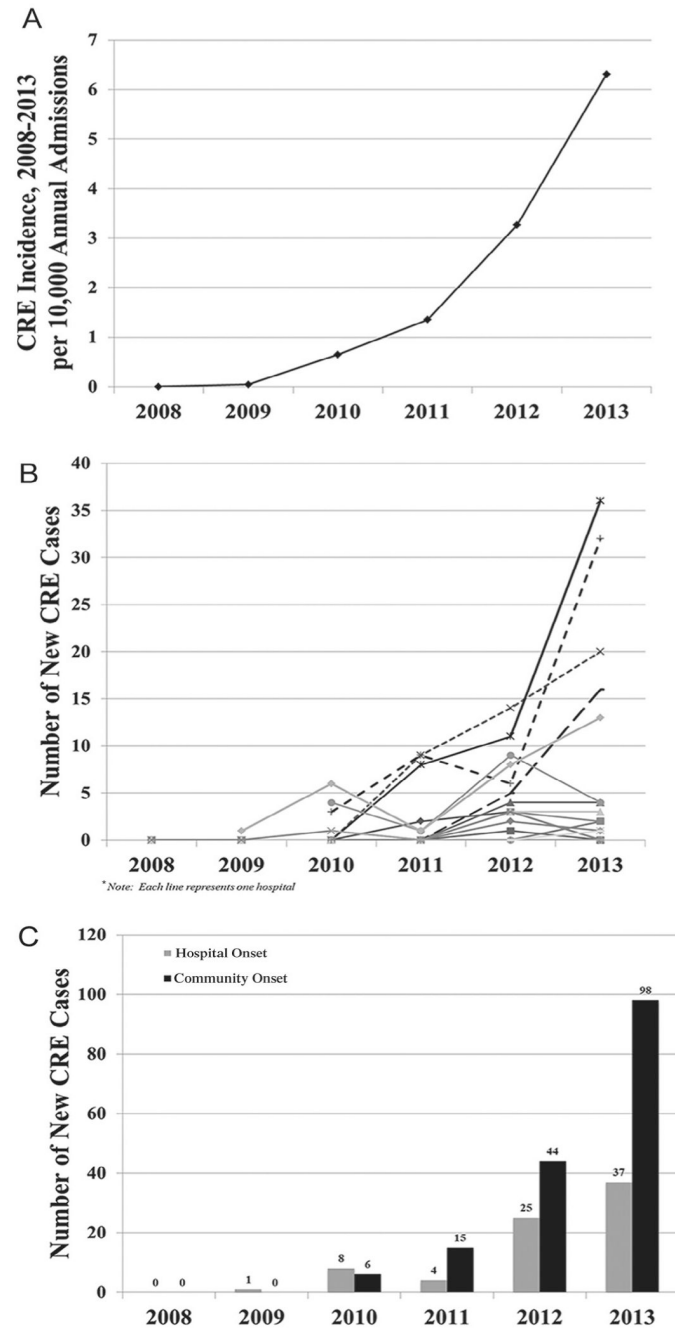
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**Fig 1.** Emergence of carbapenem-resistant Enterobacteriaceae (CRE) in Orange County, CA, 2008-2013. A, CRE incidence, Orange County, California. B, CRE incidence per hospital, with burden concentrated within a few hospitals. C, Hospital- and community-onset CRE incident cases.

**Table 1**

Characteristics of participating hospitals, Orange County, California, 2013

<b>Hospital characteristic</b>	<b>Acute care hospitals</b>
Number of beds	183 (27-457)
Number of admissions	11,120 (147-29,665)
Length of stay	4.4 (3.4-95.6)
No. of admissions by age, y	
< 18	35,926 (16.9)
19-49	65,823 (31.0)
50-65	39,532 (18.6)
66-85	52,999 (25.0)
85	17,767 (8.4)
Male gender	88,098 (41.6)
Number of admissions by race	
White	154,572 (72.9)
Black	4,707 (2.2)
Asian	28,702 (13.5)
Other	24,066 (11.4)
Number of admissions by insurance carrier	
Medicare	73,807 (34.8)
Medicaid	42,275 (19.9)
Private	75,698 (35.7)
Other	20,228 (9.6)
Mean Elixhauser Comorbidity Index score (Mean SD)	2.0(0-13)

NOTE. Values are presented as median (range) or n (%).

**Table 2**

Infection prevention strategies currently used for carbapenem-resistant Enterobacteriaceae (CRE) at participating hospitals

Infection prevention strategies currently in place for patients with CRE infection	Adoption among respondents *
Contact precautions (gown, gloves, private room, dedicated patient care equipment)	21 (100)
Notify next facility of multidrug-resistant organism detection for patient transferred to another facility	19 (90)
Patient asked to minimize leaving room	18 (86)
Notify prior facility of multidrug-resistant organism detection for patient received by transfer	14 (67)
Patient asked to wear protective gown when leaving room	12 (57)
Cohort patients with same multidrug-resistant organism in a single room	10 (48)
Active CRE screening for exposed patients	
Roommate of CRE patient	5 (28)
Neighboring room inhabitants of CRE patient	1 (6)
Roommate/neighboring rooms if CRE cluster	5 (28)
Daily chlorhexidine gluconate bathing †	4 (22)
Active effort to minimize device use	4 (22)
Active effort to minimize antibiotic use ***Active CRE screening for patients admitted	2 (11)
From long-term acute care	2 (11)
Undergoing hemodialysis	4 (6)
From nursing home	1 (6)
From other hospitals	1 (6)
With indwelling urinary catheters	0
With indwelling central line catheters	0
One-to-one nursing cohort (nurse only takes care of CRE patients)	0

NOTE. Values are presented as n (%).

\* Percentage calculated per number of respondents for each question, ranging from 86%-100% (18 to 21) response.

† One hospital had adopted housewide chlorhexidine gluconate bathing; the remainder used chlorhexidine gluconate in at least 1 intensive care unit and used chlorhexidine gluconate bathing for patients with drug-resistant organisms, including CRE.

**Table 3**

Support for strategies in a regional carbapenem-resistant Enterobacteriaceae (CRE) infection prevention collaborative

	Percentage of respondents		
	Definitely or possibly will support	Uncertain	Definitely or possibly will not support
Isolation and precautions of patients with CRE infection			
Single room isolation	100	0	0
Place in contact precautions	100	0	0
Active observation for hand hygiene and contact precautions adherence	95	5	0
Active intra- and interfacility communication			
Communicate with treating registered nurse and physician, providing education on CRE and regional collaborative efforts	100	0	0
Communicate with facilities receiving hospital patients about CRE status and regional collaborative to institute bundle	100	0	0
Prevalence screening for CRE			
Perform annual 1-d prevalence screen for CRE among all patients in 1 intensive care unit and 1 nonintensive care unit	71	10	19
Perform biannual 1-d prevalence screen for CRE among all patients in 1 intensive care unit and 1 nonintensive care unit	43	38	19
Screening nearby patients			
Screen roommate of patient found to have CRE infection	81	19	0
Screen neighboring rooms of patient found to have CRE infection	38	48	14
CRE screening of patients from other facilities			
Screen all admitted from nursing home	48	38	14
Screen all admitted from long-term acute care facilities	48	38	14
Screen all transfers from acute care hospitals	57	29	14
Daily chlorhexidine gluconate bathing for hospitalized patients with CRE infection	86	14	0