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The Importance of Long-term Acute Care Hospitals in the Regional Epidemiology of *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacteriaceae

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Abstract

Background.—In the United States, *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae are increasingly detected in clinical infections; however, the colonization burden of these organisms among short-stay and long-term acute care hospitals is unknown.

Methods.—Short-stay acute care hospitals with adult intensive care units (ICUs) in the city of Chicago were recruited for 2 cross-sectional single-day point prevalence surveys (survey 1, July 2010–January 2011; survey 2, January–July 2011). In addition, all long-term acute care hospitals (LTACHs) in the Chicago region (Cook County) were recruited for a single-day point prevalence survey during January–May 2011. Swab specimens were collected from rectal, inguinal, or urine sites and tested for Enterobacteriaceae carrying *bla*_{KPC}.

Results.—We surveyed 24 of 25 eligible short-stay acute care hospitals and 7 of 7 eligible LTACHs. Among LTACHs, 30.4% (119 of 391) of patients were colonized with KPC-producing Enterobacteriaceae, compared to 3.3% (30 of 910) of short-stay hospital ICU patients (prevalence ratio, 9.2; 95% confidence interval, 6.3–13.5). All surveyed LTACHs had patients harboring KPC (prevalence range, 10%–54%), versus 15 of 24 short-stay hospitals (prevalence range, 0%–29%). Several patient-level covariates present at the time of survey—LTACH facility type, mechanical ventilation, and length of stay—were independent risk factors for KPC-producing Enterobacteriaceae colonization.

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Conclusions.—We identified high colonization prevalence of KPC-producing Enterobacteriaceae among patients in LTACHs. Patients with chronic medical care needs in long-term care facilities may play an important role in the spread of these extremely drug-resistant pathogens.

Keywords

carbapenem-resistant Enterobacteriaceae; *Klebsiella pneumoniae* carbapenemase; healthcare epidemiology; long-term care facilities; intensive care units

Carbapenem-resistant Enterobacteriaceae, which cause infections with limited treatment options and high mortality, are a major public health concern [1]. The most common carbapenemase in the United States is *Klebsiella pneumoniae* carbapenemase (KPC); since its first report in 2001, it has increasingly caused clinical infections worldwide [2, 3].

Outbreaks of KPC-producing Enterobacteriaceae were initially described among short-stay acute care hospitals, including in high prevalence regions such as New York City and Israel [4, 5]. Subsequently, KPC-producing Enterobacteriaceae were recognized among long-term care facilities [6]; in particular, single-center outbreaks have been linked to long-term acute care hospitals (LTACHs), defined by the Centers for Medicare and Medicaid Services as acute care hospitals with a mean length of stay > 25 days [7-9]. In the United States, LTACHs have been implicated as potential facilitators of KPC transmission across interconnected healthcare facilities [10-13].

Regional epidemiologic evaluations of KPC-producing Enterobacteriaceae that include different types of healthcare facilities are needed to coordinate infection control efforts. In the United States, such evaluations have relied on surveillance of microbiologic cultures obtained for clinical purposes [2, 5, 14-16]. However, surveillance of clinical cultures does not adequately detect asymptomatic carriers of KPC-producing Enterobacteriaceae; to characterize the entire burden of colonization, point prevalence surveys that include asymptomatic patients are needed.

In 2010, we utilized an ongoing regional multidrug-resistant organism surveillance network involving intensive care units (ICUs) of short-stay acute care hospitals to ascertain the prevalence of colonization by KPC-producing Enterobacteriaceae in our region. We additionally recruited all regional LTACHs into the surveillance network. We hypothesized that LTACH patients, who frequently have risk factors for multidrug-resistant organism carriage, would have a higher rate of colonization with KPC-producing Enterobacteriaceae compared to ICU patients in short-stay acute care hospitals.

METHODS

Facility and Patient Recruitment

In 2010, we recruited short-stay acute care hospitals with > 10 ICU beds in the city limits of Chicago, Illinois, to participate in point prevalence surveys for colonization of KPC-producing organisms. Since 2008, these facilities were already participating in twice-yearly point prevalence surveys directed at methicillin-resistant *Staphylococcus aureus*. For KPC

surveillance, 2 point prevalence surveys were performed in adult ICUs at each participating short-stay acute care hospital, approximately 6 months apart. Survey 1 occurred between July 2010 and January 2011; survey 2 occurred between January 2011 and July 2011.

In addition, all LTACHs in Cook County, which includes Chicago and its immediate surrounding suburbs, were recruited for a single-day point prevalence survey between January and May 2011.

Culture and Data Collection

On each point prevalence survey day, a central project coordinator provided all standardized culturing and data tracking materials as well as on-site training and coordination. Local hospital staff (primarily infection preventionists, with help from ward nurses if available) as well as the central project coordinator performed the patient-level specimen collection. Patients who were present in their ICU room at the time of the surveillance visit were considered eligible for participation. Written informed consent was waived for this project, but patients who were competent were provided a standardized verbal explanation of the rationale for surveillance and were asked for verbal assent.

The first 6 short-stay acute care hospitals of the first survey period used the following surveillance protocol: each patient had a swab specimen collected from a 10 × 10-cm inguinal region using a sterile dry rayon swab (BD BBL CultureSwab, Fisher Scientific, Pittsburgh, Pennsylvania); in addition, if an indwelling urinary catheter bag was present, urine from the bag was collected in a sterile urine cup, then sampled using a calibrated 0.01-mL sterile loop. The rationale of using nonrectal anatomic sites was to improve facility and patient acceptance of KPC surveillance by avoiding rectal culturing.

However, after early feedback from participating hospitals indicating feasibility of including rectal cultures, and because of our desire to utilize rectal culturing as the most sensitive single site for detection of gram-negative colonization [17, 18], we modified the surveillance protocol partway through the first survey period. For all remaining short-stay acute care hospitals (n = 18) in the first survey, as well as all short-stay acute care hospitals in the second survey (n = 24) and LTACHs (n = 7), KPC surveillance involved performing a rectal culture using a dry rayon swab. Alternatively, in lieu of a rectal culture, a culture could be obtained from the perirectal area (if visible stool was present) or from a fecal incontinence bag. If a patient declined a rectal culture but agreed to skin culturing, we obtained a swab specimen from a 10 × 10-cm inguinal region using a sterile dry rayon swab. All swabs were transported to the central laboratory in liquid Stuart medium.

At the time of specimen collection, the following patient characteristics were assessed: age (in years), ICU or LTACH length of stay (in days), sex, mechanical ventilation, and contact precautions status.

Laboratory Methods

All culture swabs were processed in a central laboratory within 6 hours of collection. Each culture sample was tested for KPC-producing Enterobacteriaceae using a direct ertapenem disk method [19]. Broth enrichment was not performed. Isolated colonies from positive cultures were tested for *bla*_{KPC} using real-time polymerase chain reaction (PCR) [20], which

included a universal bacterial 16S ribosomal RNA gene as an internal control [21]. All direct ertapenem disk screen-positive isolates, regardless of *bla*_{KPC} status, were identified to the species level and tested for antibiotic susceptibility using the MicroScan Walkaway System (Siemens); isolates nonsusceptible to any of the 3 carbapenems tested (imipenem, meropenem, or ertapenem) [22] and resistant to all of the following third-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime) [22] were classified as carbapenem-resistant Enterobacteriaceae, based on the interim surveillance definition used by the Centers for Disease Control and Prevention (CDC) [23]. Aminoglycoside susceptibility (gentamicin, tobramycin, amikacin) was classified according to Clinical and Laboratory Standards Institute breakpoints [24]. Tigecycline and colistin minimum inhibitory concentrations (MICs) were determined by Etest (bioMérieux, Durham, North Carolina). Isolates were considered susceptible to tigecycline and colistin if the MIC was $\leq 2 \mu\text{g/mL}$ [25,26].

Statistical Analyses

For bivariable analyses, we used the χ^2 test or Fisher exact test to compare categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. Exact binomial methods were used to calculate 95% confidence intervals for prevalence rates. We reported differences in prevalence rates using the prevalence ratio. We assessed the following covariates, measured at the time of the point prevalence survey, for their association with the outcome of being colonized with KPC-producing Enterobacteriaceae: LTACH facility type (vs short-stay acute care hospital ICU), mechanical ventilation, length of stay (natural log-transformed due to extreme positive skew), age (each additional year), and male sex. Univariate and multivariable analyses were performed using Poisson regression with robust variance to calculate relative risk. The multivariable model was derived using backward selection with manual interpretation of removal effect on the primary predictor of interest, long-term acute care facility. All 2-way interaction terms, including interactions by facility type (LTACH vs short-stay acute care hospital ICU), were assessed. All data were analyzed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina).

Ethical Review

This project underwent ethical review at the CDC and was determined to be a nonresearch activity. Therefore, it was not subject to a review by the CDC institutional review board. The project was also evaluated independently at each participating healthcare facility and either deemed a public health assessment or human subjects research and approved by local review boards where applicable.

RESULTS

In total, 24 of 25 eligible short-stay acute care hospitals and 7 of 7 eligible LTACHs participated in the point prevalence surveys. The median adult ICU bed size for participating short-stay acute care hospitals was 19 beds (range, 10–127 beds; interquartile range [IQR], 12–35.5 beds), and for LTACHs, the median facility bed size was 109 beds (range, 86–164 beds; IQR, 94–129 beds).

The overall participation rate among patients was high and similar across 2 survey periods among short-stay acute care hospitals: in survey 1, 448 of 490 patients participated (91%) and in survey 2, 462 of 510 patients participated (91%). The patient participation rate among LTACHs was high, 391 of 406 (96%).

Participating patient characteristics differed between short-stay acute care hospitals and LTACHs (Table 1). The median length of stay at the time of the point prevalence survey, mean patient age, proportion of patients with mechanical ventilation, and proportion of patients in contact precautions was higher among LTACH patients compared to short-stay acute care hospital patients.

Among short-stay acute care hospital patients, surveillance cultures were obtained from a variety of anatomic sites: in survey 1, the most common site was rectum (52%) followed by inguinal plus urine (24%), inguinal only (23%), and urine only (2%), whereas in survey 2, the most common site was rectum (82%) followed by inguinal only (18%). Among LTACH patients, all patients were tested with rectal cultures (100%).

Among short-stay acute care hospitals, the overall KPC colonization prevalence was 3.3% (30/910; 95% confidence interval [CI], 2.2%–4.7%) across both surveys (Figure 1). There was no significant difference between survey 1 and 2 (3.8% [17/448] versus 2.8% [13/462], respectively; $P = .46$). For LTACHs, the overall KPC colonization prevalence was 30.4% (119/391; 95% CI, 25.9%–35.3%). The overall prevalence rate of KPC colonization among LTACH patients was 9-fold higher than that of short-stay acute care hospital ICU patients (prevalence ratio, 9.2; 95% CI, 6.3–13.5; $P < .001$). Comparisons between short-stay acute care hospital ICUs and LTACHs using the CDC's interim surveillance definition for CRE showed a similar trend: CRE prevalence was 4.2% (38/910) among short-stay acute care hospital ICU patients versus 32.4% (127/391) among LTACH patients.

Fifteen of 24 short-stay acute care hospitals had at least 1 KPC-colonized ICU patient across either survey; individual short-stay acute care hospital prevalence rates (combining surveys 1 and 2) ranged from 0% to 29%. In contrast, 7 of 7 LTACHs had KPC-colonized patients; individual LTACH prevalence rates ranged from 10% to 54%.

The likelihood of being KPC positive was not significantly different between patients tested rectally versus extrarectally. Among short-stay acute care hospital patients, KPC prevalence rate among patients with rectal cultures only was 3.6% (22/591) compared to 2.7% (8/289) among patients with extrarectal testing only ($P = .56$).

We assessed whether KPC-positive patients as identified by point prevalence survey were already on contact precautions for any reason. Among the 30 KPC-positive short-stay acute care hospital patients identified in the point prevalence surveys, 80% ($n = 24$) were already in contact precautions for any reason, while among 119 KPC-positive LTACH patients, 95% ($n = 113$) were already on contact precautions for any reason ($P = .06$ for difference between short-stay acute care hospitals and LTACH contact precautions rate).

We assessed for unadjusted and adjusted associations between patient covariates and risk of being colonized with KPC-producing Enterobacteriaceae (Table 2). In a multivariable

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model, covariates independently associated with greater relative risk of KPC colonization included LTACH facility (vs short-stay acute care hospital ICU), mechanical ventilation, and length of stay. We did not find significant interactions in the model; thus, patient-specific risk factors for KPC colonization did not differ between LTACH and short-stay acute care hospital settings.

The species distribution of KPC-producing Enterobacteriaceae was similar between short-stay acute care hospitals and LTACHs, and thus data are presented in aggregate. Among 149 KPC-colonized patients, 87% (n = 129) carried KPC-producing *Klebsiella pneumoniae*; the remaining KPC-producing species included *Enterobacter aerogenes* (6%), *Escherichia coli* (4%), *Enterobacter cloacae* (0.7%), and co-colonization with *Klebsiella pneumoniae* plus either *E. coli* or *E. cloacae* (2.7%).

Among 149 KPC-positive patients, we recovered 170 KPC-producing isolates and performed susceptibility testing (Table 3). With respect to the 3 key antibiotic classes used for treatment of KPC-producing Enterobacteriaceae infection (aminoglycosides, glycylcyclines [tigecycline], and polymyxins [colistin]), 35% of isolates were susceptible to 2 classes or fewer, and 1% (2 isolates) were nonsusceptible to all 3 classes.

DISCUSSION

To study the epidemiology of KPC-producing Enterobacteriaceae throughout a large metropolitan region, we performed cross-sectional point prevalence surveys among patients in short-stay acute care hospital ICUs as well as LTACHs. We detected an extremely high colonization prevalence of KPC-producing Enterobacteriaceae among LTACH patients (close to 1 in 3 patients), which was 9-fold higher than that of short-stay acute care ICU patients. Our findings suggest that patients with chronic high-acuity medical care needs in long-term care facilities are a major reservoir of KPC-producing Enterobacteriaceae in healthcare systems.

In the United States, LTACHs specialize in the care of patients who have experienced a prolonged critical illness, and who remain too ill to be transferred to a lower-acuity setting. Such patients often have risk factors associated with carriage of multidrug-resistant organisms, such as advanced age, medical comorbidities, high severity of illness, high device utilization, exposure to antimicrobials, and prolonged hospitalization [7,27-30].

Our findings of high KPC prevalence among Chicago-area LTACHs generalize to other geographic regions experiencing rising levels of KPC-producing Enterobacteriaceae. LTACHs previously have been identified in single-facility outbreaks of KPC in a variety of locations, with single-facility prevalence rates up to 49% [9, 11, 31]. Furthermore, in Los Angeles County, passive surveillance of carbapenem-resistant *Klebsiella pneumoniae* among clinical cultures identified incidence rates that were 8-fold higher among LTACHs (2.54 per 1000 patient-days) compared to that of short-stay acute care hospitals (0.31 per 1000 patient-days) [14]. US surveillance of hospital-acquired infections through the National Healthcare Safety Network in 2012 found that 17.8% of LTACHs had reported carbapenem-resistant Enterobacteriaceae versus 3.9% of short-stay acute care hospitals [16].

Last, in Israel, KPC prevalence rates of 12% were found among patients in post-acute care facilities; these patients had lower medical acuity compared to patients in US LTACHs [6].

The association between LTACHs and high KPC prevalence rates likely results from their care of a patient population that is chronically and severely ill; in our LTACH study cohort, 52% of patients required chronic mechanical ventilation. We previously demonstrated that patients transferred from “skilled nursing facilities” (non-LTACH) to short-stay acute care hospitals had differential risks of KPC colonization depending on whether or not the nursing facility provided ventilator care; patients transferred from skilled nursing facilities with ventilator care had a higher rate of KPC colonization that was comparable to that of patients transferred from LTACHs [13]. In the present study, we found that patient-specific factors such as mechanical ventilation and length of stay were independent risk factors associated with being KPC-colonized at the time of the point prevalence survey. Nevertheless, being in an LTACH was an independent risk factor of KPC colonization in our multivariable model, suggesting that there may be important facility-related attributes (such as local infection control practice or nurse-patient ratios) that are also influencing KPC colonization rates.

The microbiology of KPC-producing Enterobacteriaceae among LTACHs and short-stay acute care hospitals was similar; specifically, *K. pneumoniae* represented the majority (87%) of KPC-carrying species. Many KPC-producing strains identified in our survey were extensively drug resistant, with 35% susceptible to 2 of the 3 key antimicrobial options of last resort (aminoglycosides, glycylcyclines [tigecycline], and polymyxins [colistin]).

The study has several limitations. We did not perform point prevalence surveillance among patients on short-stay acute care hospital non-ICU wards or skilled nursing facilities. Subsets of these patients may also be reservoirs for KPC, particularly skilled nursing facilities that care for mechanically ventilated patients. Furthermore, although rectal/stool culturing is the single most sensitive method for detecting KPC colonization, we initially utilized a modified protocol involving inguinal and urine culturing to detect KPC colonization, potentially decreasing sensitivity of KPC detection among a subset of patients. We were reassured that there was no significant difference in the KPC prevalence rates between the first 2 short-stay acute care hospital surveys (first survey, 3.8% vs second survey, 2.8%) even as the second survey utilized a higher rate of rectal culturing. Last, because of the wide scope of the point prevalence surveys, we limited patient covariates to those easily collected at the bedside. Although we used measures to capture patient severity of illness (such as mechanical ventilation and length of stay), there may be residual confounding in our multivariable model.

In conclusion, we identified a high colonization prevalence of KPC-producing Enterobacteriaceae among patients in LTACHs. Patients admitted from high-KPC-prevalence healthcare facilities are at heightened risk of infection with KPC-producing Enterobacteriaceae and can act as sources of KPC spread to other patients, which should inform decisions regarding empiric antibiotic treatment, targeted admission screening policies, and presumptive contact isolation. Where KPC-producing Enterobacteriaceae have spread throughout an entire region, infection control responses (such as surveillance, enhanced interfacility communication, and bundled prevention measures) need to be

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regional as well, involving both short-stay and long-term care facilities. Developing effective infection prevention measures for KPC-producing Enterobacteriaceae among our most chronically ill patients will be critical in controlling the spread of this extremely drug-resistant pathogen.

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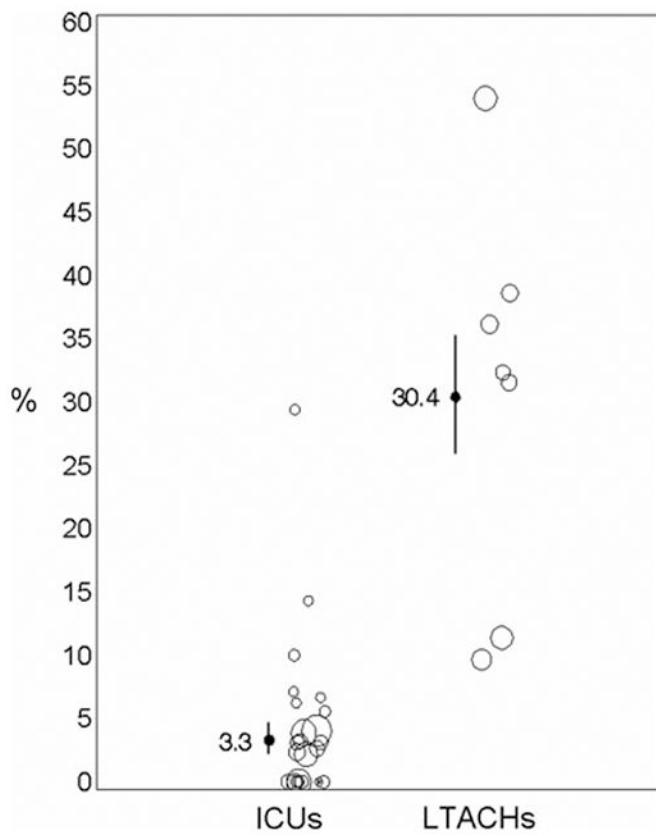


Figure 1.
Colonization prevalence of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae among patients in short-stay acute care hospital intensive care units versus long-term acute care hospitals. Solid dots represent aggregate colonization rates, with error bars representing 95% confidence intervals. Each bubble represents a single facility, with bubble size proportional to the number of patients participating in the point prevalence surveys. Short-stay acute care hospitals were surveyed twice; results were aggregated into a single summary prevalence per facility for purpose of this figure. Abbreviations: ICU, intensive care unit; LTACH, long-term acute care hospital.

Table 1.

Patient Characteristics at Short-Stay Acute Care Hospital Intensive Care Units and Long-term Acute Care Hospitals

Covariate	Short-Stay Acute Care Hospital Intensive Care Unit	Long-term Acute Care Hospital	P Value
Length of stay, median, d (IQR)	4 (2-9)	20 (11-40)	<.001
Male, no./No. (%)	504/910 (55)	213/389 (55)	.83
Age, mean y	60.0	65.9	<.001
Mechanical ventilation, no./No. (%)	311/904 (34)	203/390 (52)	<.001
Contact isolation, no./No. (%)	240/908 (26)	281/390 (72)	<.001

Abbreviation: IQR, interquartile range.

Lin et al. Page 13
Table 2.
 Associations Between Patient Covariates Present at the Time of the Point Prevalence Survey and Risk of Being Colonized With *Klebsiella pneumoniae* Carbenemase-Producing Enterobacteriaceae

Covariate	Unadjusted (Univariate)			Adjusted (Multivariable)		
	Relative Risk	95% CI	P Value	Relative Risk	95% CI	P Value
LTACH facility type (vs acute care hospital ICU)	9.23	6.30–13.53	<.001	5.94	3.75–9.39	<.001
Mechanical ventilation	3.02	2.19–4.16	<.001	1.99	1.47–2.70	<.001
Length of stay (day, log-transformed)	1.98	1.70–2.31	<.001	1.36	1.17–1.60	<.001
Age (each additional y)	1.00	.99–1.02	.35	0.99	.99–1.00	.12
Male sex	1.02	.75–1.39	.89			

Abbreviations: CI, confidence interval; ICU, intensive care unit; LTACH, long-term acute care hospital.

Table 3.

Key Antibiotic Susceptibilities Among All *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacteriaceae Isolates Tested (N = 170)

Antibiotic Class	No. (%)
Any aminoglycoside (gentamicin, tobramycin, or amikacin) susceptibility	149 (88)
Glycylcycline (tigecycline) susceptibility	138 (81)
Polymyxin (colistin) susceptibility	156 (92)
Combined aminoglycoside, glycylcycline, and polymyxin susceptibility	
Susceptible to all 3 classes	110 (65)
Susceptible to 2 classes	53 (31)
Susceptible to 1 class	5 (3)
Susceptible to 0 classes	2 (1)