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MAJOR ARTICLE

A Prospective Observational Study of the Epidemiology, Management, and Outcomes of Skin and Soft Tissue Infections Due to Carbapenem-Resistant *Enterobacteriaceae*

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Background. This study was performed to characterize the epidemiology, management, and outcomes of skin and soft tissue infection (SSTI) and colonization due to carbapenem-resistant *Enterobacteriaceae* (CRE).

Methods. Patients from the Consortium on Resistance Against Carbapenem in *Klebsiella* and Other *Enterobacteriaceae* (CRACKLE-1) from December 24, 2011 to October 1, 2014 with wound cultures positive for CRE were included in the study. Predictors of surgical intervention were analyzed. Molecular typing of isolates was performed using repetitive extragenic palindromic polymerase chain reaction (PCR). Carbapenemase genes were detected using PCR.

Results. One hundred forty-two patients were included: 62 had SSTI (44%) and 56% were colonized. Mean age was 61 years, and 48% were male: median Charlson score was 3 (interquartile range, 1–5). Forty-eight percent of patients were admitted from long-term care facilities (LTCFs), and 31% were from the community. Two strain types (ST258A and ST258B) were identified (73% of 45 tested). Carbapenemase genes were detected in 40 of 45 isolates (bla_{KPC-3} [47%], bla_{KPC-2} [42%]). Sixty-eight patients (48%) underwent surgical intervention, 63% of whom had SSTI. Patients admitted from LTCFs were less likely to undergo surgical intervention (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.18–0.71). In multivariable analysis, among patients with SSTI, those admitted from LTCFs were less likely to undergo debridement (OR, 0.18; 95% CI, 0.04–0.93).

Conclusions. Patients admitted from LTCFs with CRE SSTI were less likely to undergo surgical intervention. Sixteen percent of the patients died, and approximately 50% of survivors required more intensive care upon discharge. These findings suggest a unique, impactful syndrome within the CRE infection spectrum. Further studies are needed to assess the role of surgical debridement in management of CRE-SSTI, particularly among LTCF residents.

Keywords. carbapenem-resistant *Enterobacteriaceae*; *Klebsiella pneumoniae*; ST258; surgical site infections; wound infection.

The management of wounds may be associated with acquisition or emergence of resistance among bacteria that infect or colonize these wounds [1–3]. Often, chronic wounds occur in patients who are already at increased risk for carriage of multidrug-resistant organisms (MDROs), due to the presence of comorbid conditions as well as frequent exposures to healthcare systems and antimicrobials [1]. Furthermore, chronic wounds can foster the emergence and persistence of MDROs due to poor vascular supply and biofilm production, which limits the ability of antimicrobials to achieve therapeutic concentrations within the wound microbiome [3–5].

Carbapenem-resistant *Enterobacteriaceae* (CRE) are recognized by the US Centers for Diseases Control and Prevention (CDC) to be an urgent public health threat [6]. Carbapenem-resistant *Enterobacteriaceae* are reported to be important pathogens in wound infection in several regions including in the Middle East, Asia, and South and North America [7–10]. In addition to fostering the growth of bacteria and emergence of resistance, bacterial wound infection itself impedes the healing process [2, 11]. Given the limited antimicrobial options for

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treatment of CRE, wound infections caused by CRE may be particularly challenging to manage.

Surgical debridement has an important role in the therapeutic management of infected wounds. Debridement involves removing necrotic tissue and improving vascular supply, as well as lowering the burden of pathogens and their associated biofilm [12]. Wound debridement has been shown to improve wound healing [1, 12–15], and it might be particularly crucial for the treatment of soft tissue infections (SSTIs) due to CRE, where medical treatment options are limited. To date, the impact of surgical intervention is not yet described in patients with complex SSTIs due to CRE.

The objectives of this study were to characterize the epidemiology and management of patients with SSTI and/or colonization due to CRE in a US clinical consortium. In addition, predictors of outcome, surgical intervention, and debridement were assessed. Our analyses in this chronically ill and debilitated population uncovered unexpected findings regarding surgical interventions and outcomes.

METHODS

Study Design, Setting, and Variables

The Consortium on Resistance Against Carbapenem in *Klebsiella pneumoniae* and Other *Enterobacteriaceae* (CRACKLE) is a prospective multicenter consortium that includes the participation of 18 hospitals that are part of 8 healthcare systems predominantly located in the Great Lakes region of the United States [16]. Initially, the consortium included patients with only carbapenem-resistant *K pneumoniae* (CRKP). Since October 2014, other CRE species were also included.

This study evaluated a nested cohort within the CRACKLE-1 consortium cohort. All hospitalized patients between December 2011 and February 2016 who had skin or soft tissue (wound) cultures growing CRE were included. Each patient was included once at the time of their first CRE-positive wound culture. Patients were evaluated for the presence of SSTI. One type of SSTI was surgical site infection (SSI). Cultures derived from surgical wounds were defined as a SSI when they met CDC/National Healthcare Safety Network criteria [17]. The other type of SSTI was infection present in nonsurgical wounds, which was determined to be present when there was a positive wound culture, documentation of infection by the treating physician, as well as an evidence of inflammation on the day of positive culture (defined as an abnormal white blood cell count [>10 000 or <4000 cells/μL] and/or abnormal body temperature [>99.5°F or <96°F]). Surgical and nonsurgical wound cultures that did not meet criteria for infection were categorized as colonizers.

Data pertaining to patients' demographics and comorbid conditions, including Charlson's score index [18], admission source, discharge disposition, as well as antimicrobial treatment, antimicrobial susceptibilities of CRE, Pitt bacteremia score at the day of positive culture (which has been previously been validated as a predictor of mortality in patients with CRKP infections) [16, 19, 20], and surgical interventions were prospectively collected. Number of effective antimicrobial agents administered was captured. Ceftazidime-avibactam, tigecycline, and colistin were assumed to be effective when in vitro susceptibility was not available. Long-term care facility (LTCF) included both long-term acute care (LTAC) and skilled nursing home (SNF). Clinical outcomes that were collected included in-hospital mortality, duration of hospitalization, and discharge disposition categorized as "worsened". Worsened discharge disposition was defined as surviving patients who were discharged to a location that was associated with requiring "more intensive care" compared with their admission source (eg, home to an LTCF, home to other hospital, LTCF to hospital, SNF to LTAC). The Institutional Review Boards of all of the healthcare systems involved approved this study.

Microbiology

Carbapenem-resistant *Enterobacteriaceae* was defined, according to the Clinical and Laboratory Standard Institute (CLSI) guidelines [21], as *Enterobacteriaceae* resistant to 1 or more of the following carbapenems: imipenem, meropenem, or ertapenem. Bacterial identification and routine antimicrobial susceptibilities were performed using MicroScan (Siemens Healthcare Diagnostics) or Vitek 2 (bioMérieux) supplemented by a GN4F Sensititre tray (Thermo Fisher Scientific) to confirm carbapenem susceptibility results.

Detection of Carbapenemase Genes in Carbapenem-Resistant *Enterobacteriaceae* and Strain Typing

Carbapenem-resistant *Enterobacteriaceae*-associated carbapenemase genes were detected by polymerase chain reaction (PCR) amplification of bla_{KPC}, $bla_{NDM,}$ bla_{VIM}, bla_{IMP}, and bla_{OXA-48} genes using established primers as previously described [22]. For molecular typing of CRE, repetitive extragenic palindromic PCR (rep-PCR) were used to identify similarities among isolates. In brief, rep-PCR was conducted using the DiversiLab strain typing system (Bacterial BarCodes; bioMérieux, Athens, GA) isolates. Similarity of 95% or greater were considered to be of the same rep-PCR type [23, 24]. Multilocus sequence typing was performed on CRKP isolates from the predominant rep-PCR types, as previously described [25].

Data Analysis

Risk Factor Analysis.

Risk factor analyses were conducted, including comparing patients who underwent surgical intervention with patients who did not require surgical intervention during the study period, using the Wilcoxon rank-sum test or Student's *t* test for continuous variables and Fisher's exact test or χ^2 test for dichotomous and nominal variables. Correlation coefficients were determined using the Pearson correlation coefficient. Multivariable risk factor analyses were performed using logistic regression, to identify predictors of surgical intervention.

To assess the independent effect of admission from an LTCF on the likelihood of undergoing surgical intervention, a propensity score predicting the likelihood of admission from an LTCF was computed by comparing patients admitted from LTCFs with those not admitted from LTCFs. A multivariable logistic regression was built, and a propensity score was developed by summing together the β-coefficients of variables in the model. To determine the independent impact of admission from an LTCF on surgical intervention, a multivariable logistic regression model predicting the likelihood of surgical intervention was constructed, and the propensity score and admission from an LTCF were analyzed as independent variables.

Outcomes Analysis.

Bivariable outcomes analyses were performed to evaluate the impact of surgical intervention on in-hospital mortality and worsened disposition using the statistical tests described above. For the latter outcome, only patients who survived were included in the analysis. In addition, predictors of in-hospital mortality were assessed, and associations between SSTI and outcomes (compared with colonization) were assessed in bivariable analysis.

Multivariable Modeling

For all multivariate analyses, variables with $P < .2$ in bivariable analysis were evaluated for inclusion in multivariable models. The final models included variables with $P < .05$. Confounding variables were defined as variables that changed the β-coefficient of one of the variables in the final model by 10% or more. Variables were evaluated for confounding and, if identified as confounders, were retained in the final model, regardless of their P value. Multivariable analyses of in-hospital mortality and worsened disposition were performed using logistic regression; multivariable analysis of duration of hospitalization was performed using linear regression, after log transformation of this outcome variable. For multivariable predictors of log duration of hospitalization, the inverse natural log of the β-coefficients was calculated for variables in the final regression model and was referred to as the multiplicative effect (ME) [26]. $P < .05$ was considered to be statistically significant, and all P values were 2-sided.

RESULTS

Overall Cohort Description

One hundred forty-two patients were identified with positive soft tissue cultures for CRE (Table 1), 138 (97%) of which were CRKP, 3 were carbapenem-resistant (CR) *Enterobacter* spp, and 1 was CR *Citrobacter* spp. Sixty-two (44%) patients met criteria for a diagnosis of SSTI and 80 (56%) were colonized. Characteristics of colonized and infected patients were similar, except that significantly more infected patients had postsurgical wounds than did colonized patients (41.9% and 21.3%, respectively; $P = .01$) (Supplementary Table 1), and that surgical intervention was more common in infected patients (see below). The mean age of patients was 61 years (±17 years), 48% were male, and 56% were white. The median Charlson's score was 3 (range, 0–9). Diabetes mellitus was documented in 55% of patients. Seventy-nine (56%) patients were admitted from an LTCF.

The most common wound type was a pressure ulcer (34%) followed by postoperative wound infection (SSI; 30%). Wounds were mostly located in the extremities (27%) followed by the sacrum (24%). The majority of cultures were poly-microbial (66%), and 44 (31%) patients had CRE from other sources, including urine, blood, and respiratory tract. Most of patients received antimicrobial treatment (73.9%), and approximately half of the subjects were treated with at least 1 antibiotic with in vitro efficacy. No significant differences in antibiotic treatment between colonized and infected patients were observed (Supplementary Table 1). The median duration of hospitalization was 2 days (0–9), 22 patients (15.5%) died in-hospital, and 41 (29%) had worsened discharge disposition.

Of the 142 cultures, 45 CRE isolates were available for molecular strain typing as well as carbapenemase gene determination. Carbapenemase genes were detected in 40 isolates, 21 (47%) of which had $bla_{\text{KPC-3}}$, and 19 (42%) had $bla_{\text{KPC-2}}$. Among *K. pneumoniae* isolates carrying bla_{KPC}, the 2 predominant strain types were ST258B and ST258A (18 [40%] and 15 [33%], respectively) [16, 22].

Surgical Intervention

Surgical debridement was performed in 68 patients (48%), half of whom (n = 34) underwent debridement in the operating room (Table 1). Forty-three of 62 infected patients (69.3%) underwent surgical debridement of the wound in comparison to 25 of 80 (31.2%) colonized patients ($P < .001$).

Predictors of surgical intervention in the bivariable analysis are presented in Tables 1 and 2. In multivariable analysis (Table 3), independent predictors of surgical intervention included presence of SSI (odds ratio [OR], 9.60; 95% confidence interval [CI], 2.85–32.39) as well as SSTI without SSI (OR, 2.72; 95% CI, 1.13–6.53) (reference group for both was subjects without infection). Undergoing surgical intervention is less likely for those admitted from LTCF than those admitted from other sources (OR, 0.36; 95% CI, 0.18–0.71). This model was controlled for the confounding effects of isolating CRE from extremity wounds. In a subgroup analysis including only patients with SSTI (n = 62), admission from an LTCF remained associated with a decreased likelihood to undergo surgical debridement (OR, 0.18; 95% CI, 0.04–0.93).

Propensity-Adjusted Analysis of the Association Between Admission From a Long-Term Care Facility and Surgical Intervention

To further explore the association between admission from an LTCF and surgical intervention in the entire cohort, a propensity score was developed predicting the probability of being admitted from an LTCF. Variables associated with admission from an LTCF that were included in the propensity score

Table 1. Demographic Characteristics of Cohort and Bivariable Analysis of Predictors of Surgical Intervention

Characteristics	Entire Cohort N (%) N = 142	Surgical Intervention N (%) N = 68	No Surgical Intervention N (%) N = 74	OR (95% CI)	*P* Value
Demographics					
Age (mean ± SD)	68.3 ± 17.1	59.5 ± 17.3	62.9 ± 16.8		.24
Female	74 (52)	38 (55.9)	36 (48.6)	1.34 (0.69–2.56)	.41
Race					.22
African American	53 (37)	28 (41.2)	25 (33.8)		
Hispanic	3 (2.1)	2 (2.9)	1 (1.4)		
White	80 (55.9)	36 (52.9)	44 (59.5)		
Unknown	5 (3.5)	2 (2.9)	3 (4.1)		
Comorbid conditions					
Diabetes mellitus	75 (52.8)	33 (48.5)	42 (56.8)	0.72 (0.37–1.39)	.4
Immunocompromised	19 (13.4)	11 (16.2)	8 (10.8)	1.6 (0.6–4.2)	.46
Creatinine at baseline >2 mg/dL	41 (28.8)	24 (35.3)	17 (23)	1.83 (0.88–3.8)	.14
Charlson's score (mean ± SD)	3.5 ± 2.4	3.54 ± 2.5	3.4 ± 2.4		.79
Pitt score >3	45 (31.7)	28 (41.2)	17 (23)	2.35 (1.14–4.85)	.029
Patient Origin					.018
Home	45 (31.6)	26 (38)	19 (25.7)		
SNF	69 (48.6)	25 (36.8)	44 (59)		
LTAC	10 (7)	4 (5.9)	6 (8.1)		
Hospital transfer	14 (10)	19 (19.1)	5 (6.8)		
LTCF (SNF or LTAC) vs others	79 (55.6)	29 (42.6)	50 (67.6)	0.36 (0.18–0.71)	.004
Patient Location on Day of First Positive Wound Culture					.35
ED	22 (15.5)	9 (13.2)	13 (17.6)		
ICU	49 (22.2)	22 (32.4)	27 (36.5)		
Medical ward	49 (22.2)	22 (32.4)	27 (36.5)		
Surgical ward	12 (8.4)	8 (11.8)	4 (5.4)		
Other	10 (7)	7 (10.3)	3 (4.1)		
Time from admission to culture (median, days)	2 (0–9)	3 (0–10.5)	1 (0–9)		.26

Abbreviations: CI, confidence interval; ED, emergency department; ICU, intensive care unit; LTAC, long-term acute care; LTCF, long-term care facility; OR, odds ratio; SD, standard deviation; SNF, skilled nurse facilities.

included Charlson's score greater than 2, pressure ulcer wound type, polymicrobial culture, immunosuppression, and presence of SSI. In multivariable analysis controlling for the effects of propensity score, admission from an LTCF was no longer significantly associated with a decreased likelihood of undergoing surgical intervention (OR, 0.49; 95% CI, 0.22–1.11; $P = .09$).

Outcomes and Surgical Intervention

Mortality and Worsened Discharge Disposition

Twenty-two (15.5%) patients died during hospitalization, and 41 patients (34% of those subjects who survived) required higher level of supportive care when they were discharged, compared with the care they required before admission.

In bivariable analysis, predictors of in hospital mortality included immunosuppression (OR, 8.38; 95% CI, 2.82–24.90), Pitt score greater than 3 (OR, 8.18; 95% CI, 2.93–22.87), and prolonged duration of hospitalization before the first positive culture (median durations of 1 day, interquartile range [IQR] = 0–7 for survivors, and 15 days, IQR = 2–41 for those who died; $P < .0001$). Patients who were admitted from an LCTF were less likely to die (OR, 0.30; 95% CI, 0.11–0.80).

Associations between surgical intervention and in-hospital mortality and between surgical intervention and worsened disposition at discharge in were not observed (OR = 1.14, 95% CI, 0.46–2.85 and OR = 0.73, 95% CI, 0.34–1.56, respectively in bivariable analyses). In a subgroup analysis of patients with SSTI (N = 62), surgical intervention was not associated with in-hospital mortality (OR, 1.05; 95% CI, 0.28–3.28).

Duration of Hospitalization

The median duration of hospitalization for the subjects in the cohort was 13 days (6.75–25.25). In bivariable analysis, surgical intervention was associated with an increased duration of hospitalization ($P = .025$). In multivariable analysis, the impact of surgical intervention was evaluated, after controlling for the differences between those patients who underwent surgical debridement and those who did not (ie, controlled for admission from LTCF, Pitt score, wound location, wound type, and SSTI). Surgical intervention was not significantly associated with duration of hospitalization (ME, 1.1; 95% CI, 0.80–1.52).

Table 2. Clinical Characteristics and Management of Cohort, and Bivariable Analysis of Predictors of Surgical Intervention

Characteristics	Entire Cohort N (%) N = 142	Surgical Intervention N (%) N = 68	No Surgical Intervention N (%) N = 74	OR (95% CI)	*P* Value
Wound Type					.057
Pressure ulcer	48 (33.8)	22 (32.4)	26 (35.1)		
Postsurgical	41 (33)	26 (35.1)	21 (28.4)		
Traumatic	5 (3.5)	4 (5.9)	1 (1.4)		
Diabetic foot ulcers	12 (8.5)	9 (13.2)	3 (4.1)		
Other	34 (23.9)	11 (16.2)	23 (31.1)		
Wound location					.034
Extremities	39 (27.5)	24 (35.3)	15 (20.3)		
Sacrum	35 (24.6)	14 (20.6)	21 (28.4)		
Abdomen	7 (4.9)	1 (1.5)	6 (8.1)		
Other	61 (42.9)	29 (42.6)	32 (43.2)		
SSTI, including SSI	62 (43.7)	43 (63.2)	19 (25.7)	4.97 (2.43–10.2)	<.001
SSI, excluding other types of SSTI[a]	26 (24.5)	22 (46.8)	4 (6.8)	12.1 (3.77–38.81)	<.001
Poly-microbial wound culture	97 (68.3)	43 (63.2)	54 (73)	0.64 (0.31–1.29)	.28
Other sources of CRE in study patients					.74
Urine	26 (16.2)	8 (11.8)	15 (20.3)		
Respiratory	6 (4.2)	3 (4.4)	3 (4.1)		
Blood	13 (9.2)	7 (10.3)	6 (8.1)		
Other	2 (1.4)	1 (1.5)	1 (1.4)		
Antimicrobial agents receive within 7 days of the positive culture					
Tigecycline	58 (40.9)	25 (36.8)	33 (44.6)	0.72 (0.37–1.42)	.39
Amikacin	15 (10.6)	6 (8.8)	9 (12.2)	0.70 (0.24–2.08)	.59
Gentamicin	13 (9.2)	8 (11.8)	5 (6.8)	1.84 (0.57–5.93)	.39
Colistin	13 (9.2)	6 (8.8)	7 (9.5)	0.93 (0.30–2.91)	1.0
TMP-SMZ	11 (7.8)	7 (10.3)	4 (5.4)	2.01 (0.56–7.19)	.35
Ceftazidime/ avibactam	5 (3.5)	3 (4.4)	2 (2.7)	1.66 (0.27–10.26)	.67
Received any antimicrobial	105 (73.9)	52 (76.5)	53 (71.6)	1.29 (0.61–2.74)	.57
Received at least 1 effective antimicrobial	69 (48.6)	34 (50.0)	35 (47.3)	1.11 (0.58–2.15)	.87
Received >1 effective antibiotic	17 (12.0)	7 (10.3)	10 (13.5)	0.73 (0.26–2.05)	.61
Antimicrobial Resistance Phenotypes					
Tigecycline resistance	38 (40.4)	19 (41.3)	19 (39.6)	1.07 (0.47–2.45)	1.0
Amikacin resistance	28 (33.3)	16 (42.1)	12 (26.1)	2.06 (0.82–5.17)	.16
Gentamicin resistance	66 (47.8)	30 (45.5)	36 (50)	0.83 (0.43–1.63)	.61
Colistin resistance	7 (10.9)	2 (5.4)	5 (18.5)	0.25 (0.04–1.41)	.12
TMP-SMZ resistance	91 (65.9)	41 (63.1)	50 (68.5)	0.79 (0.39–1.59)	.59
Molecular data (n = 45)					
repPCR Clone Type					.87
Clone A	15 (33.3)	6 (30)	9 (36)		
Clone B	18 (40)	8 (40)	10 (40)		
Other clones	12 (26.7)	6 (30)	6 (24)		
Carbapenemase Gene					.92
bla_{KPC-2}	19 (42.2)	8 (40)	11 (44)		
bla_{KCP-3}	21 (46.7)	10 (50)	11 (44)		
Negative	5 (11.1)	2 (10)	3 (12)		

Abbreviations: CI, confidence interval; CRE, carbapenem-resistant *Enterobacteriaceae*; OR, odds ratio; PCR, polymerase chain reaction; SSI, surgical-site infection; SSTI, skin and soft tissue infection; TMP-SMZ, trimethoprim-sulfa-methoxazole.

[a]SSI (n = 26) was compared with colonized patients (n = 80); 47 subjects were included in the surgical intervention group and 59 in the nonintervention group

Outcomes and Colonization Versus Infection Status

Outcomes were similar in the colonized and infected groups, although patients with infection had a significantly longer median duration of hospitalization than did colonized patients (14 [IQR, 9–41] and 11 [IQR, 6–22.5]; $P = .01$) (Supplementary Table 2).

DISCUSSION

To our knowledge, this study represents the largest published cohort of CRE soft tissue infection and/or colonization. Subjects in this cohort possessed a high severity of both chronic and acute illness, which is in line with other published studies

Table 3. Multivariable Analysis: Independent Predictors of Surgical Intervention

Predictors	Adjusted OR	95% CI	*P* Value
Admission from an LTCF	0.43	0.20–0.95	.036
SSI	9.60	2.84–32.48	<.0001
SSTI without SSI[a]	2.72	1.13–6.53	.03
Pitt score >3	2.27	0.97–5.26	.058
Extremities	2.19	0.88–5.36	.085

Abbreviations: CI, confidence interval; LTCF, long-term care facility; OR, odds ratio; SSI, surgical-site infection; SSTI, skin and soft tissue infection.

[a]SSTI excluding SSI.

of other types of CRE infection [16, 27]. Of particular interest, the majority of patients arrived from LTCFs, which has been reported in other studies [28, 29] and raises concerns regarding interfacility CRE spread.

It is notable that outcomes of patients with CRE wound infection and/or colonization were generally very poor. Approximately 16% of subjects died during hospitalization, and approximately one half of subjects who survived were discharged to a location where they needed more supportive care compared with the one from which they were admitted. The degree to which these poor outcomes were attributable to CRE as opposed to other competing conditions is not yet apparent. Nevertheless, these outcomes are very serious because the burden suffered from CRE SSTIs is high. Abboud et al [8] described a cohort of 33 patients with postsurgical mediastinitis due to CRE, mainly CRKP. The mortality rate was higher in their cohort (33%) probably due to the poor outcomes associated with mediasinits [8].

We observed that approximately one half of subjects underwent surgical debridement. Surgical debridement, which involves the removal of foci of infection and necrotic or nonviable tissue, is widely recognized as an important component of the wound healing process [13, 30, 31].

It is interesting to note that subject admitted from an LTCF were significantly less likely to undergo debridement compared with subjects admitted from other sites. This association remained statistically significant in subanalysis restricted to subjects with infection, and it trended toward statistical significance in propensity-adjusted multivariable analysis of the entire study cohort. The reason for this association is not clear, but it might relate in part to an increased likelihood of debridement for SSI compared with other types of SSTIs (patients with SSI were significantly more likely to undergo debridement compared with patients with other types of SSTI [OR, 3.93; 95% CI, 1.12–13.78]) and the greater incidence of SSI in the non-LTCF population (28.6%) compared with the LTCF population (10.1%). Nevertheless, in multivariable analysis, after controlling for SSI, the LTCF population remained significantly less likely to undergo debridement. Other explanations might be a decreased clinical need for therapeutic debridement in LTCF subjects (possibly due to wound care performed in the LTCF) and/or a bias by clinicians to avoid surgical intervention in LTCF subjects. Such a bias might be due to a perception by clinicians that LTCF subjects were poor operative candidates and/or that clinical outcomes were poor for this group regardless of them receiving surgical intervention. This bias towards LTCF patients might not have been fully accounted for by other variables in the study (such as Charlson Score and Pitt Bacteremia Score).

Another possibility why LTCF patients might have been less likely to undergo debridement is that there were differences in the virulence of copathogens isolated with CRE from subjects living in an LTCF, SNF, or LTAC compared with community dwellers.

Debridement is an important component of management of both infected and noninfected wounds. Because removal of infected foci of CRE infection has been associated with improved clinical outcomes (such as mortality) [31], it is important that LTCF subjects are objectively and thoroughly evaluated for surgical debridement of infected wounds.

Our study has some limitations. As a nested cohort study, the analysis was not designed primarily to evaluate SSTIs and therefore lacked data pertaining to wound healing and staging. In addition, the retrospective nature of our review precluded the ability to assess patients' functional status and clinical progress. Moreover, only a minority of study isolates were available for molecular analysis.

CONCLUSIONS

In summary, this study demonstrated that a large proportion of the cohort was admitted from LTCFs, and debridement of wounds occurred at a lower frequency in this population compared with the population of patients not admitted from LTCFs. This finding has potential importance from not only a clinical management perspective but also from an infection prevention perspective, because wounds can serve as mobile reservoirs for CRE, facilitating dissemination of CRE across healthcare settings. In future studies, prospectively identified and monitored cohorts could provide important information regarding the impact CRE SSTIs and the role of surgical debridement in CRE-SSTI cure, particularly among patients admitted from LTCFs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. Clin Microbiol Rev **2001**; 14:244–69.
2. Halbert AR, Stacey MC, Rohr JB, Jopp-McKay A. The effect of bacterial colonization on venous ulcer healing. Australas J Dermatol **1992**; 33:75–80.
3. Akers KS, Mende K, Cheatle KA, et al. Biofilms and persistent wound infections in United States military trauma patients: a case-control analysis. BMC Infect Dis **2014**; 14:190.
4. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev **2002**; 15:167–93.
5. Vuotto C, Longo F, Balice MP, et al. Antibiotic resistance related to biofilm formation in *Klebsiella pneumoniae*. Pathogens **2014**; 3:743–58.
6. Antibiotic Resistance Threats in the United States, 2013. Available at: https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=11. Accessed 24 August **2017**.
7. Lerner A, Solter E, Rachi E, et al. Detection and characterization of carbapenemase-producing *Enterobacteriaceae* in wounded Syrian patients admitted to hospitals in northern Israel. Eur J Clin Microbiol Infect Dis **2016**; 35:149–54.
8. Abboud CS, Monteiro J, Stryjewski ME, et al. Post-surgical mediastinitis due to carbapenem-resistant *Enterobacteriaceae*: clinical, epidemiological and survival characteristics. Int J Antimicrob Agents **2016**; 47:386–90.
9. Rana MM, Sturdevant M, Patel G, Huprikar S. *Klebsiella* necrotizing soft tissue infections in liver transplant recipients: a case series. Transpl Infect Dis **2013**; 15:E157–63.
10. Bhat V, Gupta S, Kelkar R, et al. Bacteriological profile and antibiotic susceptibility patterns of clinical isolates in a tertiary care cancer center. Indian J Med Paediatr Oncol **2016**; 37:20–4.
11. Renner R, Sticherling M, Rüger R, Simon J. Persistence of bacteria like *Pseudomonas aeruginosa* in non-healing venous ulcers. Eur J Dermatol **2012**; 22:751–7.
12. Johnston BR, Ha AY, Kwan D. Surgical management of chronic wounds. R I Med J (2013) **2016**; 99:30–3.
13. Wilcox JR, Carter MJ, Covington S. Frequency of debridements and time to heal: a retrospective cohort study of 312 744 wounds. JAMA Dermatol **2013**; 149:1050–8.
14. Wong SY, Manikam R, Muniandy S. Prevalence and antibiotic susceptibility of bacteria from acute and chronic wounds in Malaysian subjects. J Infect Dev Ctries **2015**; 9:936–44.
15. Howell-Jones RS, Wilson MJ, Hill KE, et al. A review of the microbiology, antibiotic usage and resistance in chronic skin wounds. J Antimicrob Chemother **2005**; 55:143–9.
16. van Duin D, Perez F, Rudin SD, et al. Surveillance of carbapenem-resistant *Klebsiella pneumoniae*: tracking molecular epidemiology and outcomes through a regional network. Antimicrob Agents Chemother **2014**; 58:4035–41.
17. CDC/NHSN Surveillance Definition of Healthcare-Associated Infection and Criteria for Specific Types of Infections in the Acute Care Setting. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf. Accessed 24 August **2017**.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
19. Neuner EA, Yeh JY, Hall GS, et al. Treatment and outcomes in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. Diagn Microbiol Infect Dis **2011**; 69:357–62.
20. Hauck C, Cober E, Richter SS, et al. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect **2016**; 22:513–9.
21. Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. JAMA **2013**; 309:275–82.
22. Endimiani A, Hujer AM, Perez F, et al. Characterization of blaKPC-containing *Klebsiella pneumoniae* isolates detected in different institutions in the Eastern USA. J Antimicrob Chemother **2009**; 63:427–37.
23. Versalovic J, Koeuth T, Lupski JR. Distribution of repetitive DNA sequences in eubacteria and application to fingerprinting of bacterial genomes. Nucleic Acids Res **1991**; 19:6823–31.
24. Zhou T, Zhang X, Guo M, et al. Phenotypic and molecular characteristics of carbapenem-non-susceptible *Enterobacteriaceae* from a teaching hospital in Wenzhou, southern China. Jpn J Infect Dis **2013**; 66:96–102.
25. Diancourt L, Passet V, Verhoef J, et al. Multilocus sequence typing of *Klebsiella pneumoniae* nosocomial isolates. J Clin Microbiol **2005**; 43:4178–82.
26. Kaye KS, Engemann JJ, Mozaffari E, Carmeli Y. Reference group choice and antibiotic resistance outcomes. Emerg Infect Dis **2004**; 10:1125–8.
27. Temkin E, Adler A, Lerner A, Carmeli Y. Carbapenem-resistant *Enterobacteriaceae*: biology, epidemiology, and management. Ann N Y Acad Sci **2014**; 1323:22–42.
28. Marchaim D, Chopra T, Bogan C, et al. The burden of multidrug-resistant organisms on tertiary hospitals posed by patients with recent stays in long-term acute care facilities. Am J Infect Control **2012**; 40:760–5.
29. Bhargava A, Hayakawa K, Silverman E, et al. Risk factors for colonization due to carbapenem-resistant *Enterobacteriaceae* among patients exposed to long-term acute care and acute care facilities. Infect Control Hosp Epidemiol **2014**; 35:398–405.
30. Cardinal M, Eisenbud DE, Armstrong DG, et al. Serial surgical debridement: a retrospective study on clinical outcomes in chronic lower extremity wounds. Wound Repair Regen **2009**; 17:306–11.
31. Patel G, Huprikar S, Factor SH, et al. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol **2008**; 29:1099–106.