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Characteristics of community-acquired carbapenem-resistant Enterobacterales

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Background: Community-acquired carbapenem-resistant Enterobacterales (CA-CRE) are an important threat.

Methods: In CRACKLE-2, we defined patients with CA-CRE as admitted from home, without pre-existing conditions, and a positive culture within 48 h of admission. Healthcare-associated CRE (HA-CRE) were those with the lowest likelihood of community acquisition, not admitted from home and cultured >48 h after admission. Specific genetic markers in carbapenemase-producing *Klebsiella pneumoniae* were evaluated through random forest modelling.

Results: CA-CRE and HA-CRE were detected in 83 (10%) and 208 (26%) of 807 patients. No significant differences were observed in bacterial species or strain type distribution. *K. pneumoniae* (204/291, 70%) was the most common CRE species, of these 184/204 (90%) were carbapenemase producers (CPKP). The top three genetic markers in random forest models were *kpi_SA15*, *fimE*, and *kpfC*. Of these, *kpi_SA15* (which encodes a chap-erone/usher system) was positively associated (OR 3.14, 95% CI 1.13–8.87, $P=0.026$), and *kpfC* negatively associated (OR 0.21, 95% CI 0.05–0.72, $P=0.015$) with CA-CPKP.

Conclusions: Ten percent of CDC-defined CRE were CA. The true proportion of CA-CRE in hospitalized patients is likely lower as patients may have had unrecorded prior healthcare exposure. The *kpi_SA15* operon was associated with the CA phenotype.

Introduction

Enterobacterales are commonly encountered pathogens causing community-associated infections, such as urinary tract infections. More recently, ESBL-producing Enterobacterales have been increasingly associated with community-acquired (CA) infections in the US and worldwide.¹ Carbapenems are the preferred

treatment option for invasive ESBL-producing Enterobacterales infections.^{2,3} Concerningly, carbapenem resistance is also increasingly observed in Enterobacterales.^{4,5} Several novel treatment options have been developed recently to better treat infections caused by carbapenem-resistant Enterobacterales (CRE).^{6–8} However, the costs, need for intravenous therapy, and concerns over further resistance development, limit the use of these

agents, especially in empirical antibiotic regimens. There are several reports of CA-CRE causing bacteraemia, gastroenteritis, urinary tract infections, neonatal meningitis, and peritonitis.^{1,9,10} In addition, in the Consortium on Resistance against Carbapenems in *Klebsiella* and other Enterobacteriales (CRACKLE) studies, the proportion of patients hospitalized with CRE who were admitted from home increased over time.^{11,12}

We have previously described 1040 unique patients hospitalized in 49 US hospitals with CRE isolated from clinical cultures.¹¹ Here, we explored possible community origins of CRE in a subset of these patients. We compared characteristics between CRE that were CA-CRE and those that were healthcare-associated (HA) CRE.

Patients and methods

Patients

CRACKLE-2 was a prospective, observational, multicentre cohort study.¹¹ For this analysis, patients were included from CRACKLE-2 who were hospitalized in participating US hospitals between 30 April 2016 and 31 August 2017 with CRE isolated from any anatomical site in a clinical culture and who met criteria for CA-CRE or HA-CRE. Patients with CRE that were susceptible to carbapenems upon centralized susceptibility testing ('unconfirmed CRE') were excluded.¹¹ The characteristics of the cohort from which these patients have been selected have been previously described.¹¹ Patients from 24 study sites were included.

Ethics

The Institutional Review Board (IRB) of each participating healthcare system approved this study. Need for informed consent was waived by each participating IRB. The IRB approval reference number at the University of North Carolina at Chapel Hill is 19-3032.

Clinical definitions

Infections were defined using standardized criteria, as previously described.¹¹ As the collected data did not allow application of the criteria outlined by the US Centers for Disease Control and Prevention, CA-CRE were defined here by the presence of all of the following: admission from home, index CRE culture date within 48 h of hospitalization, and absence of five documented conditions that would increase the likelihood of recent healthcare exposure (kidney disease, malignancy, liver disease, immunocompromise, or pregnancy). For the purpose of these analyses, HA-CRE were defined as those isolates with the lowest likelihood of community acquisition: admission from a long-term care or acute healthcare facility AND timing of index CRE culture more than 48 h after admission. Patients who fell into neither the CA-CRE nor the HA-CRE category were excluded from these analyses. Clinical data were obtained from electronic medical records, and outcomes were defined as previously described.¹¹

Microbiology

Susceptibility to carbapenems was determined at local clinical laboratories following the manufacturer's instructions for MicroScan (Beckman Coulter, Atlanta, GA, US), Vitek®2 and Etest® (both bioMérieux, Durham, NC, US), BD Phoenix™ and BBL™ discs (both Becton Dickinson, Durham, NC, US), Sensititre (Thermo Fisher, Waltham, MA, US), and using disc diffusion or in-house agar dilution tests. Carbapenem susceptibility results were confirmed in two independent central research laboratories using the Etest® and MicroScan. CRE isolates that tested susceptible to carbapenems upon central testing ('unconfirmed CRE') were excluded from this study.¹¹

Whole-genome sequencing and genomic analysis

Genomic analysis was limited to carbapenemase-producing *K. pneumoniae* (CPKP). WGS methods and genomic analyses were described previously.¹¹ Briefly, Snippy was used to identify core SNPs from whole genome sequences for each genome compared with the reference genome NGST258_2 (GCA_000597905.1). DNA sequences identified as being prophages, repeat regions, or regions of recombination were masked from downstream analysis using PHASTER, MUMmer, and Gubbins, respectively.¹³⁻¹⁵ A maximum-likelihood phylogenetic tree was constructed from the recombination-free alignment using RAxML (v8.2.12) using a general time-reversible model of nucleotide substitution and four discrete gamma categories of rate heterogeneity (GTRGAMMA). Node support was estimated by bootstrapping with 500 replicates. Clusters were defined as strains sharing <22 SNPs and a most-recent common ancestor based on the phylogenetic tree.¹⁶ R package 'circlize' was used to visualize the phylogenetic tree.¹⁷

Statistical analysis

Distributions across two groups were analysed using the Wilcoxon Rank Sum test for continuous variables and Fisher's exact or Pearson- χ^2 tests for categorical variables. *P* values <0.05 were considered statistically significant. The CRACKLE-2 desirability of outcome ranking (DOOR) was compared across groups, as previously described.¹¹ Briefly, this outcome assessed three deleterious events: lack of clinical response, prolonged hospitalization (hospitalization \geq 30 days after first positive culture or re-admission within 30 days), and adverse events (new renal failure and/or *Clostridioides difficile* infection), in addition to survival at 30 days after the index culture. The best outcome was defined as being alive without deleterious events. The worst outcome was death. Two levels in-between these two extremes were: alive with 1 event, and alive with 2 or 3 deleterious events. Within the subset of patients with CPKP (*n* = 184), random forest analysis for the purpose of variable selection was performed on bacterial genetic markers with CA-CRE versus HA-CRE as the outcome. Seventy-five markers were *a priori* hypothesized to be potentially associated with colonization based on literature review (Table S1, available as [Supplementary data](#) at JAC Online). Of these 75 markers, 40 were found in >95% or <5% of strains and were excluded from analyses. Relative importance of variables in random forest models was determined using mean decrease in Gini coefficient and mean decrease in accuracy over 10 models. Logistic regression was used to determine OR and 95% confidence intervals (CI) of the top three selected genes. SAS 9.4 (SAS Institute, Cary, NC) and R 4.1.1 (R Core Team, 2020) were used for analyses.

Results

Clinical characteristics and outcomes

In CRACKLE-2, 807 unique patients with confirmed CRE were enrolled during the study period. Of these, 83 (10%) and 208 (26%) met the criteria for either CA-CRE or HA-CRE, respectively (Table 1 and Figure 1). Distinct variability in the proportions of HA-CRE and CA-CRE of total CRE cases was observed between study sites (Figure S1, available as [Supplementary data](#) at JAC Online). Patients with CA-CRE were more likely to be admitted at a community hospital; 28% of patients with CA-CRE were admitted at a community hospital, as compared with 13% of patients with HA-CRE (*P* < 0.01). The distribution of sources between CA-CRE and HA-CRE was significantly different, *P* < 0.001; the urine was a more common source for CA-CRE (65% versus 25% in HA-CRE), whereas HA-CRE were more frequently isolated from the respiratory tract (40% versus 7% in CA-CRE). As expected,

Table 1. Patient characteristics with possibly community-associated CRE (CA-CRE) versus confirmed healthcare-associated CRE (HA-CRE)

Characteristic	CA-CRE (n=83)	HA-CRE (n=208)	Total (n=291)	P value
Region				0.24
Northeast	34 (41)	105 (50)	139 (48)	
South	25 (30)	45 (22)	70 (24)	
Midwest	18 (22)	36 (17)	54 (19)	
West	6 (7)	22 (11)	28 (10)	
Age, years, median (IQR)	64 (47–77)	65 (55–77)	65 (54–77)	0.59
Gender				0.78
Male	44 (53)	114 (55)	158 (54)	
Female	39 (47)	94 (45)	133 (46)	
Hispanic or Latino ethnicity	16 (19)	19 (9)	35 (12)	0.02
Race				0.76
White	33 (40)	97 (47)	130 (45)	
Black	27 (33)	65 (31)	92 (32)	
Other ^a	11 (13)	26 (12)	37 (13)	
Unknown	12 (14)	20 (10)	32 (11)	
Post-culture length of hospital stay, days, median (IQR)	7 (4–12)	15 (7–29)	12 (6–23)	<0.001
Charlson comorbidity score, median (IQR)	1 (0–3)	3 (1–5)	3 (1–4)	<0.001
Pitt bacteraemia score, median (IQR)	2 (0–3)	4 (2–6)	3 (2–6)	<0.001
Culture source				<0.001
Urine	54 (65)	52 (25)	106 (36)	
Wound	10 (12)	35 (17)	45 (15)	
Blood	6 (7)	18 (9)	24 (8)	
Respiratory	6 (7)	84 (40)	90 (31)	
Other	7 (8)	19 (9)	26 (9)	
Infection	30 (36)	86 (41)	116 (40)	0.41
Community hospital	23 (28)	28 (13)	51 (18)	<0.01
Disposition after discharge				<0.001
Death	3 (4)	53 (25)	56 (19)	
Hospice	2 (2)	10 (5)	12 (4)	
Home	55 (66)	25 (12)	80 (27)	
Long-term care	18 (22)	69 (33)	87 (30)	
Long-term acute care	4 (5)	38 (18)	42 (14)	
Transfer to other hospital	1 (1)	13 (6)	14 (5)	
30 day mortality	5 (6)	55 (26)	60 (21)	<0.001
90 day mortality	8 (10)	71 (34)	79 (27)	<0.001
90 day readmission	34/78 (44)	59/145 (41)	93/223 (42)	0.69
DOOR at 30 days				
Alive without events	58 (70)	66 (32)	124 (43)	
Alive with one event	19 (23)	45 (22)	64 (22)	
Alive with two or three events	1 (1)	42 (20)	43 (15)	
Dead	5 (6)	55 (26)	60 (21)	

Values shown are *n* (%) unless indicated otherwise.

^aOther races include Native Hawaiian or Pacific islander (*n*=2), Asian (*n*=29) and multiracial (*n*=69).

since absence of several comorbid conditions is part of the CA-CRE definition, the Charlson comorbidity index was lower in patients with CA-CRE (median 1, IQR 0–3) versus HA-CRE (median 3, IQR 1–5), *P*<0.001. Patients with CA-CRE had shorter post-culture hospital stays (median 7 days, IQR 4–12 days versus 15 days, IQR 7–29 days, *P*<0.001) and lower acuity of illness on the day of positive culture (median Pitt bacteraemia score 2, IQR 0–3 versus 4, IQR 2–6, *P*<0.001) than those with HA-CRE. Overall, mortality of patients with CA-CRE was significantly lower

as compared with patients with HA-CRE at 30 days (6% versus 26%, *P*<0.001) and at 90 days (10% versus 34%, *P*<0.001). Inverse probability weighting (IPW)-adjusted DOOR analysis showed that a randomly selected patient with CA-CRE had a 66% (95% CI 56%–78%) chance of a better overall outcome as compared with a patient with HA-CRE (Table 1). Similar differences were observed in the subset of patients with infections for unadjusted DOOR probabilities (69%, 95% CI 59%–78%), and for mortality at 30 days (10% versus 35%, *P*<0.001) and

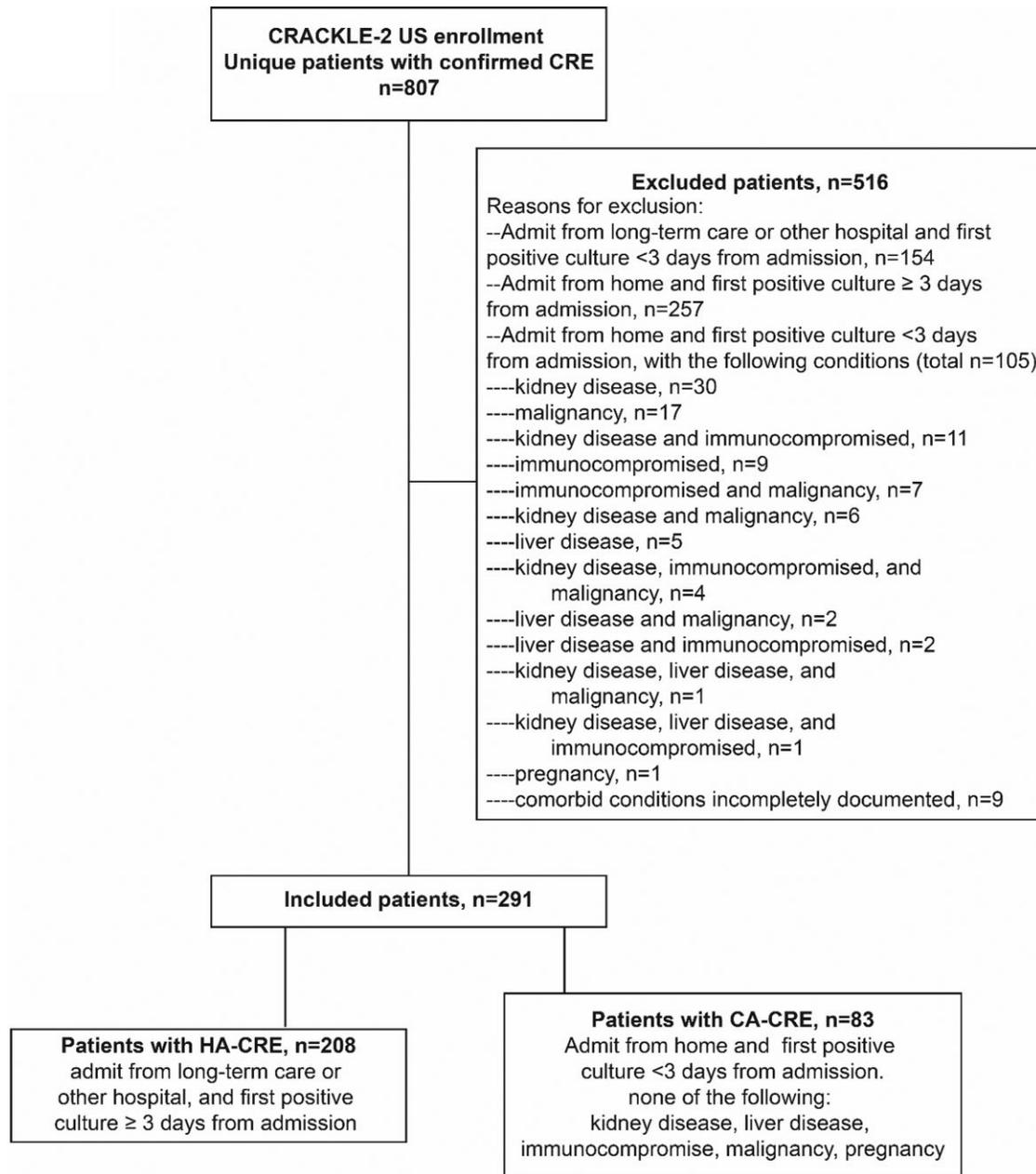


Figure 1. Flow diagram.

90 days (10% versus 42%, $P < 0.001$). Of note, 90 day readmission rates in patients discharged alive were similarly high in patients with CA-CRE (34/78, 44%) and patients with HA-CRE (59/145, 41%), $P = 0.69$.

Microbiology

The most common carbapenemase genes in both groups were *bla*_{KPC-2} and *bla*_{KPC-3}, which were found in 94% (214/227) of carbapenemase-producing Enterobacteriales (Table 2). No difference in carbapenemase gene distribution was noted between CA-CRE and HA-CRE. Species distribution was similar

between CA-CRE and HA-CRE (Table 2). Seventy percent of CRE isolates were *K. pneumoniae* (204/291), of which 66% (135/204) belonged to ST258. ST258 was similarly common in CA-carbapenem-resistant *K. pneumoniae* (CRKP) (36/60, 60%) and HA-CRKP (98/144, 68%). Carbapenemase genes were present in 90% of CRKP (184/204). In non-*K. pneumoniae* CRE, carbapenemase genes were present in 43/87 (49%) isolates; *bla*_{KPC-2} ($n = 15$) and *bla*_{KPC-3} ($n = 22$) were most commonly encountered. ST131 ($n = 15$, 68%) was the most common genetic lineage in *E. coli*, and four ST131 *E. coli* were CA-CRE. Five of 41 (12%) *Enterobacter* isolates were ST171 *E. cloacae*, of which four were CA-CRE.

Table 2. Bacterial characteristics of possibly community-associated CRE (CA-CRE) and confirmed healthcare-associated CRE (HA-CRE) isolates

Characteristic	CA-CRE (n=83)	HA-CRE (n=208)	Total (n=291)	P value
Species				0.28
<i>Klebsiella pneumoniae</i>	60 (72)	144 (69)	204 (70)	
ST258	36 (43)	98 (48)	134 (46)	
ST307	4 (5)	6 (3)	10 (3)	
ST15	3 (4)	3 (1)	6 (2)	
<i>Enterobacter</i> spp.	12 (14)	29 (14)	41 (14)	
ST171 <i>E. cloacae</i>	4 (5)	1 (0)	5 (2)	
<i>Escherichia coli</i>	8 (10)	14 (7)	22 (8)	
ST131	4 (5)	11 (5)	15 (5)	
Other <i>Klebsiella</i> spp. ^a	0 (0)	10 (5)	10 (3)	
Other ^b	3 (4)	11 (5)	14 (5)	
Carbapenemase present ^c	67 (81)	160 (77)	227 (78)	0.48
bla _{KPC-2}	37 (45)	82 (39)	119 (41)	
bla _{KPC-3}	22 (27)	75 (36)	97 (33)	
bla _{NDM-1}	5 (6)	0	5 (2)	
Other ^d	4 (5)	5 (2)	9 (3)	

Data shown are n (%) unless otherwise indicated.

^a*Klebsiella aerogenes* (n=6), *Klebsiella michiganensis* (n=3), *Klebsiella oxytoca* (n=1).

^b*Serratia marcescens* (n=5), *Citrobacter freundii* (n=4), *Raoultella ornithinolytica* (n=2), *Citrobacter freundii* (n=1), *Hafnia paralvei* (n=1), *Providencia stuartii* (n=1).

^cCounts exceed 100%, as three isolates carried two different carbapenemase genes.

^dbla_{KPC-4} (n=2), bla_{OXA-232} (n=4), bla_{NDM-7} (n=1), bla_{VIM-2} (n=1), bla_{SME-2} (n=1), bla_{OXA-181} (n=1).

Molecular epidemiology of carbapenemase-producing *K. pneumoniae*

The population structure of 184 CPKP [53 (29%) CA-CPKP and 131 (71%) HA-CPKP] is shown in Figure 2. In CPKP, 131 (71%) strains belonged to ST258, and a total of 27 K-loci types were present. Most ST258 CPKP isolates had either KL107 (64/128, 50%), KL106 (38/128, 30%), or KL51 (14/128, 11%). All ST307 isolates had KL102 (10/10, 100%). Six ST15 CPKP strain were found, three of these were CA-CPKP. The O-locus O2v2 was present in 86/184 (47%) CPKP isolates; 74/131 (56%) ST258 carried O2v2 versus 12/53 (23%) of non-ST258 isolates ($P < 0.001$). CA-CPKP and HA-CPKP had a similar distribution of K-loci and O-loci. In total, 113 CPKP belonged to 31 clusters; 26/53 (49%) of CA-CPKP and 87/131 (66%) of HA-CPKP. 16/31 (52%) of clusters contained only HA-CPKP strains (n=47), 14 clusters contained both CA-CPKP (n=26) and HA-CPKP (n=40), and a single cluster contained two CA-CPKP isolates.

Bacterial genetic analysis

Bacterial genetic markers previously reported to be potentially associated with colonization were selected based on literature review (Table S1). Results of random forest modelling are shown

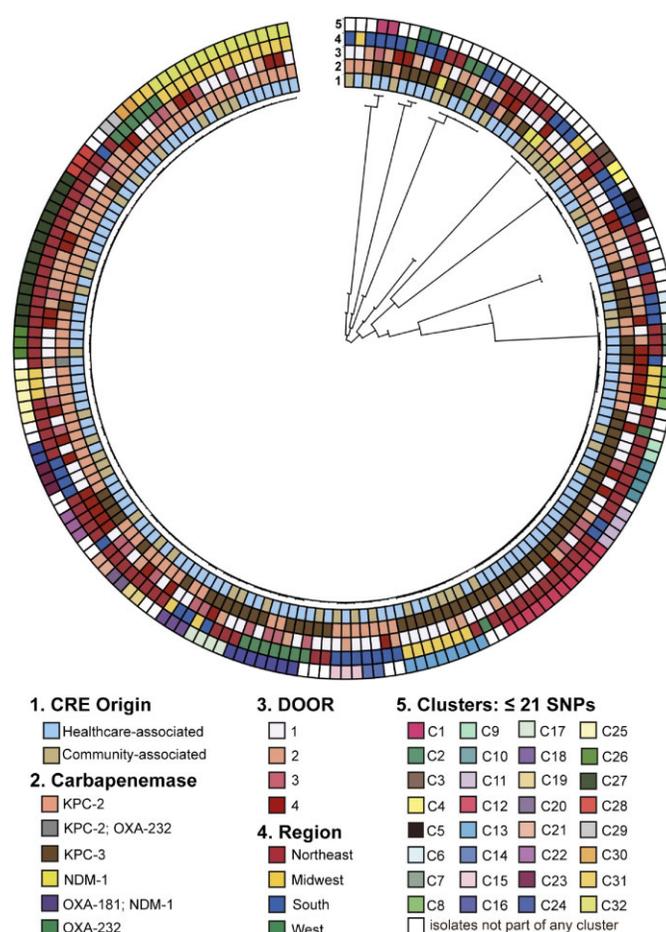


Figure 2. Maximum likelihood phylogenetic tree of carbapenemase-producing *Klebsiella pneumoniae* (n=184). DOOR outcomes (1) alive without events, (2) alive with 1 event, (3) alive with 2 or 3 events, or (4) death.

in Figure 3. The top three genetic markers associated with highest mean decreases in Gini coefficient and accuracy over 10 separate models were *kpi_SA15*, *kpfC*, and *fimE*. The *kpi_SA15* operon was more commonly present in CA-CPKP isolates (9/53, 17%) as compared with HA-CPKP (8/131, 6%), $P=0.026$. *kpfC* was less commonly present in CA-CPKP isolates (46/53, 87%) as compared with HA-CPKP (127/131, 97%), $P=0.015$. No difference in distribution of *fimE* between CA-CPKP (48/53, 91%) and HA-CPKP (121/131, 92%) was observed.

Discussion

Overall, we found that 10% of patients hospitalized with CRE represented community-associated cases. Our estimates of CA-CRE varied geographically and between participating hospitals in the same region. A rise in CA-CRE infections has been observed in other regions of the world.^{1,18,19} An international scoping review of CRE in the community reported estimates of CA-CRE proportion ranging from 0%–30%.²⁰ In the four US-based studies included in this review, estimates ranged

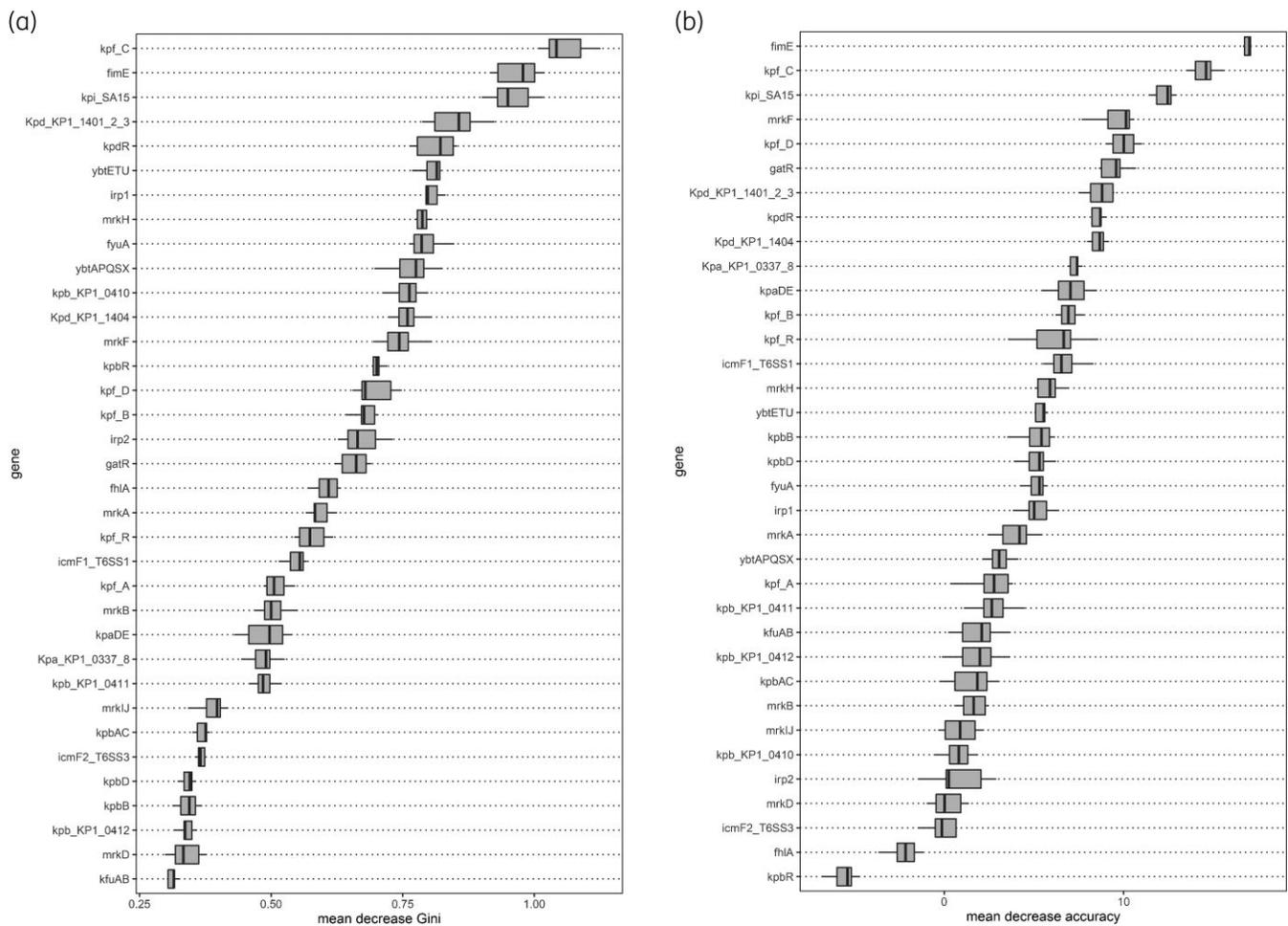


Figure 3. Results of random forest modelling. Boxes indicate the first and third quartile, line indicates the median, and whiskers indicate the minimum and maximum. Results shown for each genetic marker from 10 random forest models. (a) Decrease in mean Gini coefficient. (b) Decrease in mean accuracy.

between 5.6% and 10.8%, consistent with our findings.^{21–24} These studies were conducted between 2008–13 and used various methods and definitions of CA-CRE to arrive at their estimates.^{21–24} Between 2012 and 2017, rates of CRE cases in the US have been stable and there has been no indication of widespread community transmission of CRE in the US.²⁵ However, early recognition of CRE strains that may contribute to future community spread is of the utmost importance. A shift from predominantly healthcare-associated to community-acquired infections in the epidemiology of CRE would have a dramatic impact on our society through lives lost, increased healthcare costs, and increased antibiotic usage.

We observed several clinical differences between patients with CA-CRE and HA-CRE. This was expected, as our definition for CA-CRE not only selects for higher likelihood of community acquisition, but also for a healthier population with fewer comorbid conditions. The differences in outcomes including all-cause mortality, post-culture length-of-stay, and DOOR outcomes are most likely primarily related to host factors, rather than to reduced pathogenicity of CA-CRE. Surprisingly, rates of readmission were

similarly high in patients with CA-CRE when compared with patients with HA-CRE. This may be a consequence of the impact of the detection of CRE in clinical cultures, which is known to predispose to subsequent CRE infections.²⁶

In *E. coli*, we specifically looked for and found several CA-CRE isolates belonging to ST131. However, we did not find evidence that ST131 was overrepresented in the CA-CRE cohort. ST131 *E. coli* is a worldwide-distributed high-risk strain that is frequently associated with urinary tract infections and bacteraemia.²⁷ Multiple reports of household and pet-to-human transmission of ST131 *E. coli* have been reported.²⁷ Our cohort is limited as an evaluation of the impact of ST131 *E. coli* in community spread of CRE in the US, as only 22 patients with *E. coli* were included. While also limited by small numbers, we observed a numerical overrepresentation of ST171 *E. cloacae* in CA-CRE strains. ST171 has been previously identified as a high-risk CRE clone associated primarily with KPC-3 that is emerging in the US.²⁸ Both ST131 *E. coli* and ST171 *E. cloacae* have the potential to cause increasing numbers of CA-CRE infections in the future. Monitoring these strain types going forward is warranted.

As most patients in our cohort had carbapenemase-producing *K. pneumoniae*, we focused our in-depth genetic analyses on this subgroup. CA-CRE and HA-CRE were mixed throughout the population structure of CRE in this cohort, and we found no evidence for a single clone accounting for most of the community transmission. Several clusters were identified, including clusters that included both patients with CA-CRE and HA-CRE implying possible intra-hospital transmission of CA-CRE isolates to hospitalized patients. We hypothesized that the ability of bacteria to successfully colonize hosts with a relatively normal gut microbiome is one of the requirements for successful community spread. Therefore, we selected bacterial genetic markers *a priori* that had previously been reported to be potentially associated with colonization by *K. pneumoniae*. These included genes encoding type 1 (*fim*) and type 3 (*mrk*) pili, as well as other fimbriae operons. *fim* and *mrk* are the best described chaperone/usher systems encoding genes resulting in assembly of type 1 and type 3 fimbriae.^{29,30} *fimE* and *fimB* control phase-switching of type 1 fimbriae, and absence of *fimE* results in overexpression of type 1 fimbriae.³¹ It is unclear why *fimE* was identified as an important variable in random forest modelling as no numeric differences were found in positivity rates for *fimE* between CA-CPKP and HA-CPKP strains. In random forest analysis, a high relative importance may be a consequence of interactions with other variables. Therefore, absence of *fimE* may be important for the CA phenotype only in the setting of other specific genetic markers. The presence of the *kpi_SA15* operon was associated with CA-CRE phenotype in our cohort. This should be considered a hypothesis-generating finding. The *kpi_SA15* operon contains four genes that encode components of a different chaperone/usher system.^{32,33} However, little is known about the functional importance of this system. *kpfC* encodes the usher component of the *kpf* chaperone-usher system. *kpfR* is a negative regulator of the *kpf* system.³⁴ A *kpfR* knock-out *K. pneumoniae* strain exhibited enhanced biofilm formation, but decreased capsule production.³⁴ The associations between the CA phenotype and the *kpi_SA15* operon and *kpfC* should be further evaluated in future studies. Of these, the *kpi_SA15* operon is of higher interest given the positive association with community spread and prior studies.

Limitations

This study has several limitations. First, as a secondary analysis of the CRACKLE-2 cohort, defining CA cases was limited to the available clinical variables that may have misclassified some isolates. Documentation on prior hospitalizations, emergency room visits, and long-term care stays outside the study period was unavailable. For instance, it is possible that a patient admitted from home had a recent hospitalization or long-term care stay during which CRE was acquired. It is therefore likely that we overestimated true community acquisition of CRE. Second, our definition for CA-CRE excludes patients with a history of several clinical comorbidities indicative of healthcare exposures. Thus, it is not surprising that improved clinical outcomes were observed in patients with CA-CRE, including DOOR outcomes and survival. Third, associations with bacterial genetic markers should be considered hypothesis-generating. Future studies are required to determine whether any of the bacterial characteristics we identified are truly associated with CA-CRE.

Conclusions

In summary, community spread of CRE was limited during the study period with approximately 10% of patients meeting criteria for community acquisition. True community acquisition likely occurred only in a subset of these 10% of patients with CRE. Several high-risk strain types were identified within the CA-CRE cohort. Understanding the epidemiology of CA-CRE and at-risk people for carriage of CA-CRE strains will assist with measures to control AMR spread and early detection of community spread of CRE.

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Members of the MDRO Network Investigators

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Disclaimer

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Supplementary data

Figure S1 and Table S1 are available as [Supplementary data](#) at JAC Online.

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