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MAJOR ARTICLE

Increased Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* Within the Gut Microbiota Is Associated With Risk of Bloodstream Infection in Long-term Acute Care Hospital Patients

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Background. An association between increased relative abundance of specific bacterial taxa in the intestinal microbiota and bacteremia has been reported in some high-risk patient populations.

Methods. We collected weekly rectal swab samples from patients at 1 long-term acute care hospital (LTACH) in Chicago from May 2015 to May 2016. Samples positive for *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) by polymerase chain reaction and culture underwent 16S rRNA gene sequence analysis; relative abundance of the operational taxonomic unit containing KPC-Kp was determined. Receiver operator characteristic (ROC) curves were constructed using results from the sample with highest relative abundance of KPC-Kp from each patient admission, excluding samples collected after KPC-Kp bacteremia. Cox regression analysis was performed to evaluate risk factors associated with time to achieve KPC-Kp relative abundance thresholds calculated by ROC curve analysis.

Results. We collected 2319 samples from 562 admissions (506 patients); KPC-Kp colonization was detected in 255 (45.4%) admissions and KPC-Kp bacteremia in 11 (4.3%). A relative abundance cutoff of 22% predicted KPC-Kp bacteremia with sensitivity 73%, specificity 72%, and relative risk 4.2 (P = .01). In a multivariable Cox regression model adjusted for age, Charlson comorbidity index, and medical devices, carbapenem receipt was associated with achieving the 22% relative abundance threshold (P = .044).

Conclusion. Carbapenem receipt was associated with increased hazard for high relative abundance of KPC-Kp in the gut microbiota. Increased relative abundance of KPC-Kp was associated with KPC-Kp bacteremia. Whether bacteremia arose directly from bacterial translocation or indirectly from skin contamination followed by bloodstream invasion remains to be determined.

Keywords. carbapenemase-producing *Klebsiella pneumoniae*; microbiome; intestinal domination; bloodstream infection; long-term acute care hospital.

Overgrowth of potentially pathogenic microbes in the large intestine followed by systemic invasion (bacterial translocation) has been recognized among patients with neutropenia, inflammatory bowel disease, intestinal obstruction, and liver cirrhosis and in neonates [1–4]. Recently, sequence analysis of the gene that encodes the RNA component of the small ribosomal subunit (the 16S rRNA-encoding gene) has allowed culture-independent determination of the composition of gut bacterial communities (intestinal microbiota) in these and other patients [5]. In one study of adult allogeneic hematopoietic stem cell transplant recipients, a relative abundance of 30% or more of enterococci in the microbial community (ie, enterococcal "domination") increased the risk of vancomycin-resistant enterococcal bacteremia 9-fold, and domination by Proteobacteria increased the risk of gram-negative rod bacteremia 5-fold [6]. Similar observations have been made in preterm infants with late-onset sepsis and in children undergoing therapy for newly diagnosed acute lymphoblastic leukemia [7, 8]. While the presumed mechanism for the increased risk of blood stream infection (BSI) associated with intestinal domination in these populations is bacterial translocation, alternative mechanisms are possible. These include a cutaneous pathway in which intestinal domination increases the risk of skin colonization

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and contamination of central venous catheter exit sites or wounds followed by bloodstream invasion with or without local infection [9].

Various factors are known to influence the intestinal microbiota, including diet, host immunity, and receipt of medications including antibiotics [10, 11]. Long-term acute care hospital (LTACH) patients are at high risk of microbiota disruption due to waning mucosal immunity associated with advanced age, underlying comorbid medical conditions, and frequent antibiotic exposures [12]. In turn, a disrupted microbiota may place LTACH patients at risk of colonization or infection with antibiotic-resistant bacteria such as *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp). In Chicago, KPC-Kp is endemic in LTACHs, with colonization prevalence at some facilities as high as 50% [13, 14]. While KPC-Kp BSI has been reported in LTACH patients, an association between BSI and high relative abundance of KPC-Kp in the intestinal microbiota has not been investigated [14–16].

Here, we report results of a longitudinal study in a Chicago LTACH to examine risk factors for development of increased relative abundance of KPC-Kp in the intestinal microbiota and to determine whether increased relative abundance of KPC-Kp in the gut was associated with risk of BSI.

METHODS

Study Design and Medical Record Review

We conducted a prospective, longitudinal, observational study at a 106-bed LTACH in Chicago. We collected rectal swab samples from patients at admission and weekly from 4 May 2015 to 13 May 2016. Admissions among patients who had at least 1 swab sample positive for KPC-Kp (colonized patients) were analyzed. Clinical and microbiological data were extracted from hospital information systems. We reviewed medical records of all patients with KPC-Kp BSI to investigate the cause of bacteremia. The study was reviewed and approved by the Rush University Medical Center Institutional Review Board, to which the participating LTACH had formally ceded oversight. Informed consent was waived.

Laboratory Methods

All rectal swab samples were screened for KPC-Kp by polymerase chain reaction (PCR) [17–19]. Screen-positive samples were cultured for *K. pneumoniae* on sheep's blood and MacConkey agars. Mucoid, lactose-positive, oxidase-negative colonies underwent identification to the species level and were determined to be resistant to carbapenems by the MicroScan Walkaway System (Beckman Coulter, Indianapolis, IN). *Klebsiella pneumoniae* isolates that were confirmed to be carbapenem resistant then underwent a second round of PCR to document the presence of the bla_{KPC} gene [17–19].

DNA was purified directly from rectal swabs using the PowerMag Soil DNA Isolation Kit (Mo Bio Laboratories, Inc., Carlsbad, CA) using the EpMotion 5075 (Eppendorf, Hamburg, Germany). We have shown in a similar patient population that the fecal microbiota from rectal swabs and fecal samples collected from the same individual were highly similar, justifying the use of rectal swabs to survey the fecal microbiota in our study [20]. Dual-index primers specific to the V4 region were used to PCR amplify the bacterial 16S rRNA gene [21] from 1μL of the sample DNA, as described previously [22, 23]. Amplicons were prepared for sequencing and sequenced using the 500 cycle MiSeq Reagent Kit v2 (Illumina, catalog no. MS-102–2003) on a MiSeq (Illumina, San Diego, CA) by the University of Michigan Microbial Systems Molecular Biology Laboratory as described previously [22]. Sequences were processed and analyzed using mothur (v.1.39.5) [24]. The mothur-adapted SILVA SEED reference alignment (release 119) was used to align and trim sequences [25]. Uchime was used to remove chimeric sequences [26]. Samples with fewer than 3000 sequences after processing were excluded. For all microbiota analyses of KPC-Kp–positive samples (n = 892), a 97% sequence similarity was used to cluster sequences into operational taxonomic units (OTUs) using the average neighbor method. Relative abundance of OTUs in each sample was calculated. The Ribosomal Database Project training set (v10) was used to obtain taxonomic classification of OTUs [27]. Raw sequence data for the samples used in this project were deposited in BioProjects PRJNA485316 and PRJNA428477 (see Supplementary Table 1 for a list of BioSample accession numbers).

We determined that 1 OTU represented KPC-Kp. This OTU contained a single unique sequence that matched various Enterobacteriaceae family members, including 16S rRNA gene sequences from *K. pneumoniae*, *Klebsiella variicola*, and members of the genera *Enterobacter* and *Buttiauxella*. We observed several exact matches to at least 1 copy of the 16S rRNA gene sequence in genomes from *K. pneumoniae* strain multilocus sequence type ST258, *K. pneumoniae* subsp. *pneumoniae* ST258-K26BO, and *K. pneumonia* subsp. *pneumoniae* strain ST258_FL, confirming that the canonical KPC-Kp strains belonging to ST258 would fall into this OTU.

Statistical Analyses

Receiver operator characteristic (ROC) curves were constructed using results from analysis of the rectal sample with the highest relative abundance of KPC-Kp (reads of the OTU that contained KPC-Kp divided by the total number of reads in the sample) from each unique patient admission, excluding any samples collected after KPC-Kp bacteremia. Cox regression analysis was performed to evaluate clinical risk factors associated with the time to achieve KPC-Kp relative abundance thresholds determined by ROC curve analysis. We considered a P value of <.05 to be significant. All statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY) and R version 3.4.3 [28].

RESULTS

We collected 2319 rectal swab samples (median, 3; range, 1–18) from 562 admissions (506 patients), of whom 255 (45.4%) were colonized with KPC-Kp and 11 (4.3%) developed KPC-Kp bacteremia. Bacteremia was observed only in patients with documented KPC-Kp colonization. Mean age of KPC-Kp colonized patients was 63.2 years (standard deviation ± 15.9 years), and median length of hospital stay was 40 days (interquartile range, 27–65 days). A total of 235 (92.2%) patients received at least 1 dose of antibiotic during their LTACH stay. Other patient characteristics are summarized in Table 1.

ROC curve analysis for the relative abundance of KPC-Kp in the intestinal microbiota vs KPC-Kp bacteremia showed an area under the curve of 0.78 (95% confidence interval [CI], 0.66–0.91; $P = .002$), indicating fair predictive ability (Figure 1). A KPC-Kp relative abundance cutoff of 22% predicted KPC-Kp bacteremia with sensitivity 73%, specificity 72%, and relative risk 4.2 (95% CI, 1.3–14.0; $P = .01$). A previously published cutoff for intestinal domination by a single bacterial taxon (≥30%) [6] yielded sensitivity 64%, specificity 79%, and relative risk 6.1 (95% CI, 1.8–20.0; $P < .001$).

Temporal trends of KPC-Kp relative abundance for the 11 patients who developed KPC-Kp BSI are shown in Figure 2; clinical presentations and outcomes are summarized in Table 2. Six patients had a single positive blood culture reported and 3 patients (patients 3, 7, 9) had multiple blood cultures that grew KPC-Kp. At the time of KPC-Kp bacteremia, 1 patient (patient 1) had *Clostridium difficile* infection with abdominal distention and another patient (patient 8) had hypoxia without other clinical or radiographic evidence of pneumonia. No other bacteremic patient had organ-specific signs or symptoms of infection reported, and no patient had a microbiologically identified source of bacteremia [29]. Nine patients were reported to have a central venous catheter in place at the time of first positive blood culture. Catheters were removed from 2 patients (patients 7, 11) and catheter tips were cultured; 1 tip was positive for KPC-Kp (patient 7). No patient was neutropenic or receiving cancer chemotherapy. Four patients (patients 3, 7, 8, 9) had been receiving glucocorticoid doses equivalent to greater than 20 mg of prednisone daily for more than 2 weeks when bacteremia was identified.

Results of the investigation of risk factors for increased relative abundance (≥22%) of KPC-Kp are shown in Table 3. In Cox univariate analyses, there were no significant associations between age, comorbid medical conditions, or presence of a medical device and increased relative abundance of KPC-Kp. Among antibiotics analyzed, only preceding carbapenem use was associated with a relative abundance of KPC-Kp ≥22% (hazard ratio [HR], 2.19; 95% CI, 1.06–4.55; $P = .036$). While no clinical variables were significantly associated with achievement of domination in univariate analysis, we included 3 variables (age, Charlson comorbidity index, and any medical device) in a multivariable model to evaluate for confounding, since these factors are frequently associated with multidrug-resistant organism colonization and acquisition. The association between

Table 1. Demographic and Clinical Characteristics of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* Colonized Patients

Parameter	Value (N = 255 admissions)[a]
Age (years), mean ± SD	63.2 ± 15.9
Female sex, n (%)	106 (41.6)
Length of hospital stay in days, median (IQR)	40 (27–65)
Body mass index, mean ± SD	27.7 ± 9.9
Devices, n (%)	
Mechanical ventilation	98 (38.4)
Central venous catheter	130 (51.6)
Oral diet	97 (38.0)
Gastrostomy tube	142 (55.7)
Indwelling or suprapubic urinary catheter	159 (62.4)
Charlson score, median (IQR)	3 (2–5)
Comorbidities, n (%)	
Diabetes mellitus	123 (48.2)
Congestive heart failure	82 (32.2)
Stroke	72 (28.2)
Decubitus ulcer	193 (75.7)
End-stage renal disease on hemodialysis	35 (13.8)
Antibiotic use, n (%)	235 (92.2)
Carbapenem	102 (40.0)
Beta-lactam/beta-lactamase inhibitor	69 (27.1)
Vancomycin (intravenous)	133 (52.2)
Metronidazole	49 (19.2)

Abbreviations: IQR, interquartile range; SD, standard deviation..

[a]Number of unique admissions colonized with KPC-Kp.

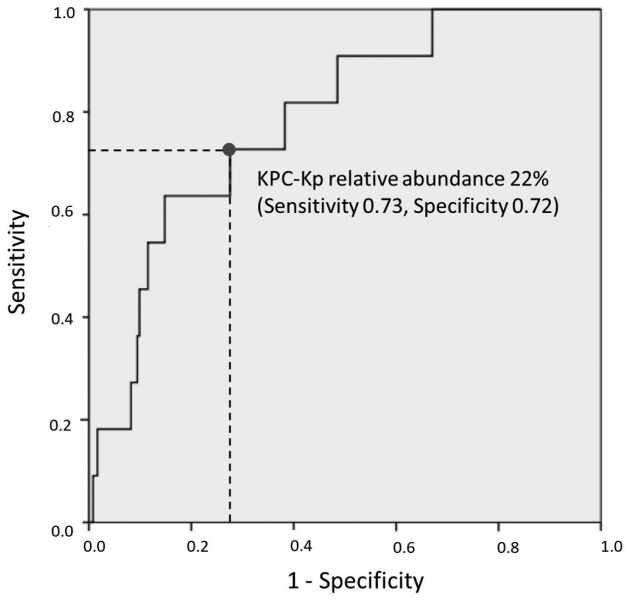

Figure 1. Receiver operating characteristic curve analysis of the relationship between relative abundance of *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) and subsequent KPC-Kp bloodstream infection. Abbreviation: KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*.

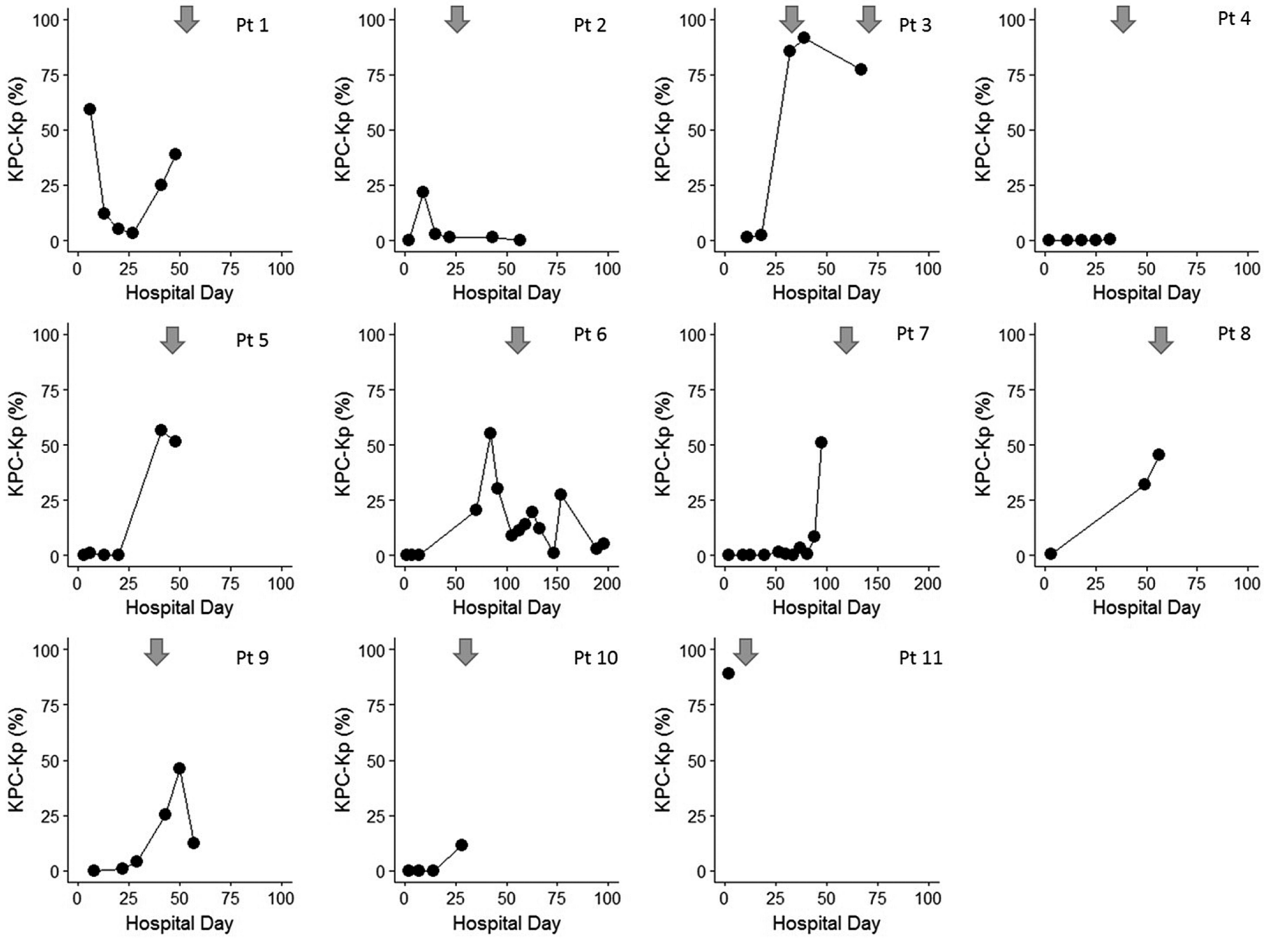

Figure 2. Chronological change of relative abundance of *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) in the gut microbiota of 11 patients with KPC-Kp bacteremia. This operational taxonomic unit (OTU) contained a single unique sequence that matched various Enterobacteriaceae family members, including the 16S rRNA gene sequences from *K. pneumoniae*. It contained several exact matches to at least 1 copy of the 16S rRNA gene sequence in genomes from several variants of *K. pneumoniae* ST258, confirming that the canonical KPC-Kp strains belonging to ST258 would fall into this OTU. Each panel shows data for a single patient's admission. Dot markers indicate the relative abundance of KPC-Kp (%) measured on the hospital day indicated. Arrows indicate date of first positive KPC-Kp blood culture. For patients with multiple positive blood cultures (patients 3, 7, 9), another arrow was added only if new infection was suspected (bacteremia episodes separated by ≥2 weeks) based on National Healthcare Safety Network surveillance definitions [29]. Abbreviations: KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*; Pt, patient.

carbapenem receipt and subsequent high relative abundance of KPC-Kp remained significant after adjustment (HR, 2.14; 95% CI, 1.02–4.49; $P = .044$).

DISCUSSION

In this single-center longitudinal study of LTACH patients who were colonized with KPC-Kp, high relative abundance of KPC-Kp in the intestinal microbiota was associated with increased risk of KPC-Kp bacteremia. Few patients had localizing signs or symptoms of infection at the time of bacteremia, no patient had a microbiologic source of bacteremia identified, and most patients (9 of 11) had a central venous catheter. Given the absence of evidence for an alternative primary source of bacteremia, the majority of BSI cases in our study would have been classified as central-line associated using National Healthcare Safety Network surveillance definitions [29]. While our clinical evaluation supports this as a potential source of bacteremia, the high relative abundance of KPC-Kp in patients' intestinal microbiota suggests that gut translocation is also a possibility, despite the absence of classic immune dysfunction or medical conditions associated with intestinal mucosal barrier injury. In a similar study, an association between central venous catheter–associated bacteremia and the intestinal microbiota was investigated in infants with small bowel syndrome and long-term parenteral nutrition, but the exact mechanism of bacteremia remained undefined [30]. Regardless of the mechanism, our findings suggest that preventing an increase in relative abundance of KPC-Kp in the gut may hold promise as a means of reducing the risk (directly or indirectly) of KPC-Kp bacteremia.

Table 2. Clinical Presentation and Outcomes for 11 Patients With *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* Bloodstream Infection

						At the Time of First KPC-Kp BSI				
						Central Venous Catheter				
ID	Sex	Age	Reason for Hospitalization	Comorbidity	Hospital Event Preceding or Concurrent With KPC-Kp BSI	Clinical Symptoms	Type	Location	Other Device	Immunosuppressants	Disposition
1	F	73	Recent pneumonia, transferred to continue care	Hypothyroidism, A fib, PVD, Pressure ulcer	*Clostridium difficile* infection	Abdominal distention, fever	PICC	Upper extremity	Tracheostomy tube, mechanical ventilator, gastrostomy tube, urinary catheter	…	Transfer to ACH
2	M	64	Recent pneumonia, cardiac arrest, transferred to continue care	COPD, pulmonary HTN	Fever followed by small bowel obstruction due to ruptured appendix	Fever	CVC	Subclavian	Tracheostomy tube, mechanical ventilator, gastrostomy tube	…	Transfer to ACH
3	F	81	Recent right groin infected hematoma around arteriovenous fistula, transferred to continue care	COPD, chronic myelogenous leukemia, ESRD on HD	General deterioration	None documented	Long-term HD catheter	Groin	Tracheostomy tube, mechanical ventilator	Glucocorticoids	Deceased
4	M	62	Recent pneumonia, transferred to continue care	COPD, DM, PVD, HTN, CHF	Septic shock during hemodialysis	Shock	Long-term HD catheter	Subclavian	Tracheostomy tube, mechanical ventilator, gastrostomy tube	…	Deceased
5	F	68	Direct admission for infected PEG tube	Ischemic stroke, MS	Persistent leak around PEG tube despite tube exchange	Fever	…	…	Tracheostomy tube, mechanical ventilator, gastrostomy tube	…	Transfer to ACH
6	F	63	Recent cardiac arrest, transferred to continue care	Asthma, CHF, obesity	Candida endocarditis, pyelonephritis, PEG tube infection	Fever	PICC	Unknown	Tracheostomy tube, mechanical ventilator, gastrostomy tube	…	Transfer to skilled nursing facility
7	F	67	Recent pneumonia, transferred to continue care	Adrenal insufficiency, COPD	Acute kidney injury requiring hemodialysis	Bradycardia	CVC, short-term HD catheter, PICC	Subclavian, internal jugular, lower extremity	Endotracheal tube, mechanical ventilator, gastrostomy tube	Glucocorticoids	Deceased
8	M	56	Recent ischemic stroke, transferred to continue care	HTN, CKD, dilated cardiomyopathy, A Fib	Respiratory failure, intubation	Hypoxia	…	…	Automated implantable cardioverter-defibrillator, gastrostomy tube	Glucocorticoids	Transfer to hospice
9	F	60	Recent left leg abscess, acalculous cholecystitis, transferred to continue care	COPD, CHF, seizure	PEG tube placement complicated by liver injury	Altered mental status, hypotension	CVC	Subclavian	Gastrostomy tube	Glucocorticoids	Transfer to ACH
10	F	73	Recent ischemic stroke, transferred to continue care	CKD, HTN, ESRD on HD, remote history of stomach cancer	Septic shock	Shock, hypoglycemia	Short-term HD catheter, port-catheter	Internal jugular, chest	Gastrostomy tube	…	Deceased
11	M	48	Recent gastrointestinal bleeding from unclear source, transferred to continue care	HTN, DM, right below knee amputation, sacral decubitus ulcer, ESRD on HD	Deep venous thrombosis around PICC line	Fever	Short-term HD catheter, PICC	Internal jugular, upper extremity	…	…	Deceased

Abbreviations: A fib, atrial fibrillation; ACH, acute care hospital; BSI, bloodstream infection; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; HD, hemodialysis; HTN, hypertension; KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*; M, male; MS, multiple sclerosis; PEG, percutaneous endoscopic gastrostomy; PICC, peripherally inserted central venous catheter; PVD, peripheral vascular disease.

Table 3. Risk Factors Associated With ≥22% Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* in the Gut Microbiota

Clinical Predictor	Hazard Ratio (95% Confidence Interval)	*P* Value
Age, years	0.99 (0.97–1.02)	.549
Charlson comorbidity index	0.90 (0.74–1.09)	.277
Any medical device use	1.05 (0.25–4.48)	.943
Mechanical ventilation	0.82 (0.39–1.71)	.588
Gastrostomy tube	0.62 (0.30–1.29)	.204
Central line	1.17 (0.55–25)	.689
Hemodialysis	0.77 (0.23–2.54)	.666
Urinary catheter	0.73 (0.34–1.55)	.409
Any antibiotic exposure	0.70 (0.24–2.07)	.519
Carbapenem	2.19 (1.06–4.55)	.036
Beta-lactam/beta-lactamase inhibitor	0.66 (0.23–1.90)	.436
Vancomycin (intravenous)	0.79 (0.38–1.66)	.537
Metronidazole	0.50 (0.12–2.12)	.351

Previous studies of immunocompromised children and adults with traditional risk factors for bacterial translocation in the gut used a relative abundance threshold of 30% as a marker of increased risk of Enterococcaceae, Streptococcaceae, and Proteobacteria bacteremia or other infections [6, 8]. Since we did not know if this threshold would apply to our patient population, we constructed an ROC curve to evaluate the sensitivity and specificity of different KPC-Kp relative abundance cutoffs for predicting KPC-Kp bacteremia. While application of the 30% KPC-Kp relative abundance threshold predicted KPC-Kp bacteremia with good specificity and reasonable sensitivity, we chose to apply a threshold of 22% since it yielded more balanced specificity and sensitivity predictions in our study cohort. It is important to recognize that both 30% and 22% relative abundances are much higher than the typical relative abundance of Enterobacteriaceae reported in healthy human intestinal bacterial communities, which is usually less than 1% [31]. Furthermore, measurement of relative abundance of OTUs in fecal or rectal swab samples may not reflect an absolute quantification of the entire intestinal bacterial community, nor does it provide information about in situ function. A more comprehensive analysis that combines 16S rRNA gene sequencing, proteomics, and metabolomics may provide better insight into the pathophysiology of bacteremia associated with increased relative abundance of KPC-Kp and other enteric bacteria.

We also evaluated clinical factors associated with microbiota compositional changes. Among the factors we evaluated, only carbapenem use was independently associated with high relative abundance of KPC-Kp. It is biologically plausible that the relative abundance of KPC-Kp increased after carbapenem exposure, which has activity against a majority of indigenous enteric bacteria but not against KPC-Kp. This finding supports the importance of antimicrobial stewardship efforts to reduce the adverse outcome of microbiome disruption, which can be associated with morbid clinical outcomes. A recent publication showed an association between exposure to broad-spectrum antibiotics and subsequent sepsis within 90 days [32]. The authors postulated that disruption of the microbiota was the potential cause of sepsis, which is consistent with our findings. Reversing antibiotic-associated microbiome disruption through interventions such as fecal microbiota transplantation or administration of beneficial microorganisms should also continue to be explored [5, 33].

Longitudinal specimen collection from a large sample of adult patients is a strength of our study, providing new insights into the chronological change of the gut microbiota in LTACH patients who are colonized with KPC-Kp [13, 14]. Our study also has several limitations. The number of patients with bacteremia was small, precluding a multivariable analysis of risk factors. Most patients (92%) received antibiotics at some point during their admission, so that we lacked a nonexposed comparator group for analysis of aggregate antibiotic effects. Rectal swab samples were collected weekly. Given the dynamic changes that occur in the gut microbiota of hospital patients, we may have missed high relative abundance of KPC-Kp in some patients, resulting in misclassification bias. We used an observational study design and conducted the study at a single LTACH, and our study patients were typical of an LTACH population with multiple comorbid medical conditions, extensive medical device use, and antibiotic exposure. These factors may limit the generalizability of our findings to non-LTACH patients. Still, that our results are consistent with those of prior studies of very different patient populations suggests that they may be relevant broadly to hospital patients.

In conclusion, we found that carbapenem use was associated with increased hazard for high relative abundance of KPC-Kp in the gut microbiota. High relative abundance of KPC-Kp was associated with KPC-Kp bacteremia. Future research should focus on investigating the mechanism of bacteremia risk and on mitigating this risk. In the meantime, our findings suggest a role for antimicrobial stewardship in limiting carbapenem use among patients who are colonized with KPC-Kp.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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Potential conflicts of interest. M. K. H. reports participation in clinical trials in which participating healthcare facilities received contributed product from Sage Products Inc., Molnlycke, Clorox, Medline, or OpGen. Neither M. K. H. nor her hospital received product, funding, or payments. M. K. H. reports receipt of an investigator-initiated research grant from Clorox,

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