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Residence in Skilled Nursing Facilities is Associated with Tigecycline Non-Susceptibility in Carbapenem-Resistant *Klebsiella pneumoniae*

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Abstract

Objective—To determine the rates of and risk factors for tigecycline non-susceptibility among carbapenem-resistant *Klebsiella pneumoniae* (CRKP) isolated from hospitalized patients.

Design—Multicenter prospective observational study

Setting—Acute care hospitals participating in the Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRaCKle)

Patients—287 patients who had CRKP isolated from clinical cultures during hospitalization

Methods—Within the study period of 12/24/2011 – 10/1/2013, the first hospitalization of each patient with CRKP was included during which tigecycline susceptibility for the CRKP isolate was determined. Clinical data was entered into a centralized database, including data on pre-hospital origin. Breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used to interpret tigecycline susceptibility testing.

Results—Of 287 patients included, 155 (54%) had tigecycline-susceptible CRKP, whereas 81 (28%) of index isolates were tigecycline-intermediate, and 51 (18%) were tigecycline-resistant. In multivariable modeling, admission from a skilled nursing facility (OR 2.51, 95% CI 1.51–4.21, p=0.0004), positive culture within 2 days of admission (OR 1.82, 95% CI 1.06–3.15, p=0.03), and receipt of tigecycline within 14 days (OR 4.38, 95% CI 1.37–17.01, p=0.02) were found to be independent risk factors for tigecycline non-susceptibility.

Conclusions—In hospitalized patients with CRKP, tigecycline non-susceptibility was more frequently seen in admissions from skilled nursing facilities and occurred earlier during hospitalization. Skilled nursing facilities are an important target for interventions to decrease antibacterial resistance to antibiotics of last resort for treatment of CRKP.

Introduction

The rise of carbapenem resistance in Enterobacteriaceae poses a global threat to the accomplishments of modern medicine[1,2]. Advances in transplant medicine, surgery, and oncology are specifically at risk. The current treatment options for infections due to carbapenem resistant Enterobacteriaceae (CRE) are very limited as most isolates are resistant to multiple classes of antibiotics. Antibacterials of last resort which are being used in the treatment of CRE include aminoglycosides, polymyxins, fosfomycin and tigecycline[3]. Novel antibiotics with activity against CRE are currently under study including the aminoglycoside plazomicin, and novel β-lactam/β-lactamase inhibitors such as ceftazidime/avibactam[4,5]. These compounds hold promise for more efficacious treatment of CRE infections combined with a more favorable side effect profile. However, development of resistance remains a concern for all current and future antibiotics as resistance may spread rapidly amongst Enterobacteriaceae through plasmids and other mobile genetic elements[6].

Causes of resistance development to various antibiotics are likely to overlap. Therefore, variables associated with tigecycline resistance, which has been increasingly observed in CRE isolates, may inform strategies to limit development of resistance against newer agents.

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In this context, we decided to study variables associated with tigecycline resistance in the Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRaCKle).

METHODS

Patients

The current study represents a nested cohort within Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRaCKle) study, that was previously described[7,8]. Briefly, CRaCKle is a prospective, observational, multicenter study which aims to study patients who have positive cultures for CRKP during their hospitalization. This nested cohort consists of all hospitalized patients who had a clinical culture which grew CRKP during their hospitalization that was tested for tigecycline susceptibility. Patients were included if their index hospitalization began and ended in the study period 12/24/2011 – 10/1/2013. Patients were included once at the time of their first positive culture. Patients who were known to be colonized with CRKP were placed in contact isolation. The Institutional Review Boards of all health systems involved approved the study.

Microbiology

CRKP are defined as *K. pneumoniae* isolates with non-susceptibility to the following carbapenems as per Clinical and Laboratory Standards Institute (CLSI) guidelines; meropenem, imipenem or ertapenem[9]. Bacterial identification and routine antimicrobial susceptibility testing was performed with MicroScan (Siemens Healthcare Diagnostics) or Vitek2 (BioMerieux), supplemented by GN4F Sensititre tray (Thermo Fisher) to confirm carbapenem results and to test tigecycline susceptibility. The majority of CRKP in CRaCKle are confirmed to carry bla_{KPC}, as previously described[8]. For interpretation of tigecycline MIC results breakpoints defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used; susceptible, intermediate, and resistant defined as MIC <2 μg/mL, 2 μg/mL, and >2 μg/mL, respectively.

Clinical Data

Clinical data was obtained from the electronic medical record, and entered into a centralized database. The index hospitalization was designated as the first hospital stay within the study period during which CRKP was isolated when the CRKP isolate was tested for tigecycline susceptibility. Standardized criteria for CRKP infection were used, as previously described[8]. Briefly, CR-Kp was isolated from blood or any other sterile source represented infection. For patients with positive respiratory cultures the criteria outlined by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) were used[10,11]. For patients with positive cultures from urine or surgical wounds, the CDC/NHSN criteria were used[12]. Critical illness was defined as a Pitt bacteremia score greater or equal to 4 points, on the day of the index culture[13]. Charlson comorbidity index was calculated[14]. The onset was considered present on admission (POA) if the first positive culture for CRKP was obtained within 48 hours of hospitalization.

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Analysis

Differences between groups were analyzed using Wilcoxon Rank Sum for continuous variables. Fisher's Exact, and Pearson testing were used for categorical variables where appropriate. A multivariable logistic regression model was constructed including all pre-culture variables that were associated with tigecycline non-susceptibility at the level of $p<0.1$ in univariate analysis. In addition, a multivariable ordinal logistic model was constructed to test associations with the ordinal outcome of tigecycline susceptibility (susceptible vs. intermediate vs. resistant). Analyses were performed using JMP software (SAS Inc, Cary, NC).

Results

Patients

During the study period, 287 patients were included. Their demographics are listed in Table 1. In this nested cohort, patients tended to be elderly with a median age of 71 years (interquartile range [IQR] 59–81 years), 63% of patients were female, and 54% were white. Comorbidities were common; the median Charlson comorbidity index was 3 (IQR 2–5), and more than half of patients had diabetes mellitus. The majority of patients were admitted from skilled nursing facilities (SNF) (53%), but 27% were admitted from home.

Cultures and timing of onset

Culture data are summarized in Table 2. Urine (61%) was by far the most common anatomic source for positive CRKP cultures. Only 44/175 (25%) of urine cultures represented a UTI. Overall, 44% of all patients met criteria for CRKP infection. Critical illness was present in 32% of patients. Critical illness at the time of first positive culture was more common in patients with CRKP infection as compared to CRKP colonization; 56/127 (44%) of patients with infection were critically ill, as compared to 37/123 (23%) of patients with colonization ($p=0.0002$). Overall length of hospital stay was prolonged at a median of 10 days (IQR 6–18 days). Remarkably, most of this hospital stay took place after the first positive CRKP culture. The median time from admission to first positive CRKP was one day (IQR 0–5 days). In 184 (64%) of patients CRKP was deemed POA. In multivariable analysis, SNF origin, anatomic source, and critical illness were associated with CRKP that were POA. POA onset was more common in patients admitted from a SNF. POA onset was noted in 112/153 (73%) patients admitted from SNF vs. in 72/134 (54%) patients admitted from other venues (OR 2.53, 95%CI 1.49–4.35, $p=0.0006$). Using respiratory source (26%) as a reference, POA onset was noted for 73%, 64%, 59%, 44% of patients with urine (OR 6.07, 95%CI 2.50–16.00), wound (OR 3.84, 95%CI 1.29–12.28), blood (OR 4.36, 95%CI 1.54–13.30), other (OR 2.24, 95%CI 0.43–11.33) anatomic sources, respectively ($p=0.0014$). In patients with critical illness, POA onset was less common; 48% vs. 72% in patients without critical illness at the time of first CRKP positive culture (OR 0.43 95%CI 0.24–0.76, $p=0.004$).

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Prior antibiotic exposure

Antibiotics used in the 14-day period preceding the first positive CRKP culture are outlined in Table 3. In the cohort as a whole, 39% of patients received at least one antibiotic in that period. The most common antibiotic used was vancomycin, which was administered to 30% of patients in the 14 days leading up to the first positive CRKP culture. Use of β-lactam/β-lactamase inhibitors (22%) and fluoroquinolones (18%) were common as well. Prior use of tigecycline was uncommon, only 6% of patients had received tigecycline.

Tigecycline susceptibility

At the time of their index culture, 132/287 (46%, 95%CI 40%–52%) of patients presented with a tigecycline non-susceptible CRKP isolate. The distribution of MICs for tigecycline is shown in Figure 1. Using univariable analysis, origin prior to admission was strongly associated with tigecycline susceptibility ($p<0.0001$). Admission from a skilled nursing facility was then compared to all other points of origin prior to hospitalization in multivariable logistic regression analysis (Table 4). In contrast, admission from LTAC was not associated with tigecycline non-susceptibility (data not shown). In this model, admission from a skilled nursing facility (OR 2.51, 95% CI 1.51–4.21, p=0.0004), POA onset (OR 1.82, 95% CI 1.06–3.15, p=0.03), and receipt of tigecycline within 14 days (OR 4.38, 95% CI 1.37–17.01, p=0.02) were found to be independent risk factors for tigecycline non-susceptibility. An ordinal logistic regression model was also constructed for the ordinal outcome of tigecycline susceptibility (i.e. susceptible vs. intermediate vs. resistant). In this model, the same variables were also found to be associated with the ordinal outcome; admission from a skilled nursing facility (p=0.0005), POA onset (p=0.0064), and receipt of tigecycline within 14 days (p=0.0094). After stratification by CRKP infection vs. colonization, admission from a skilled nursing facility remained independently associated with tigecycline non-susceptibility in multivariable analysis (OR 3.61, 95% CI 1.59–8.53, p=0.002 in patients with CRKP infection, and OR 2.38, 95% CI 1.18–4.86, p=0.015 in patients with CRKP colonization).

Discussion

In this defined cohort, predictors of tigecycline non-susceptibility in patients with CRKP include: *i)* admission from a skilled nursing facility *ii)* having an early onset of positive culture within the hospital stay; and *iii)* receipt of tigecycline in the previous 14 days. When the impact of treatment of CRKP bacteriuria on the development of tigecycline resistance was previously evaluated, we found that tigecycline treatment of the index CRKP bacteriuria was strongly associated with risk for subsequent development of tigecycline resistance (OR 6.13, 95%CI 1.15–48.65, p=0.03)[7]. In addition, this resistance was found to develop rapidly at a median of 65 days[7]. Nigo *et al.* evaluated the development of tigecycline resistance in multi-drug resistant *K. pneumoniae* (60% of these were CRKP) in a retrospective single-center case-control study[15]. They also found that tigecycline exposure was associated with the subsequent development of tigecycline resistance (OR 5.06; 95% CI, 1.80 to 14.23; p=0.002)[15]. They did not evaluate origin prior to hospitalization.

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Patients admitted from a nursing home who had a positive culture on the first or second day of hospitalization were at the highest risk of having a tigecycline-non-susceptible CRKP isolate. This finding implies that these patients came in colonized with CRKP before their hospitalization. While we cannot establish in this study where the origin is of tigecycline-non-susceptible CRKP, these findings are suggestive that either transmission of these isolates and/or *de novo* resistance mutations occur outside of the acute care setting.

In our cohort, the majority of patients with CRKP are older adults admitted from skilled nursing facilities. The presence of CRKP has been described in skilled nursing facilities outside of the US[16,17]. Within the US, CRKP has been isolated from patients transferred from LTACs and other LTCFs that provide mechanical ventilation, but recovery from patients transferred from skilled nursing facilities has been infrequently reported[18,19]. The findings from the current study suggest that CRKP might have disseminated throughout skilled nursing facilities to a greater degree than has been previously described.

The number of Americans living in nursing homes continues to increase and is currently estimated around 3 million people. The Centers for Disease Control and Prevention estimate that about 1 to 3 million serious infections occur in these patients annually, and that as many as 380,000 people die of these infections per year[20]. Most nursing home residents receive at least one course of antibiotics per year, and most courses exceed 7 days[21,22]. In addition, other risk factors for acquiring multi-drug resistant organisms are prevalent in this population as well, including frequent use of indwelling devices such as urinary catheters, chronic wounds, advanced age, and comorbidities[23].

The findings presented here suggest that nursing homes should be an increasingly important area of research and implementation of preventative strategies including infection control and antimicrobial stewardship to curtail the spread of resistance to antibiotics of last resort in CRE. Currently, tigecycline, polymyxins such as colistin, and aminoglycosides given as monotherapy or in combination with carbapenems are believed to represent the cornerstone of treatment of CRE infections[3,24]. Novel agents including novel aminoglycosides such as plazomicin and various β-lactam/ β-lactamase inhibitor combinations are currently under study and will hopefully become available for widespread clinical use soon[4,5]. As the first of such agents, ceftazidime/avibactam was recently approved by the Food and Drug Administration (FDA). However, resistance to these agents will likely develop over time as well, and is likely to be related to similar risk factors[23]. Therefore, taking action to limit spread of tigecycline resistant isolates will likely limit resistance development to novel anti-CRE antimicrobials as well. Worryingly, resistance to ceftazidime/avibactam has already been reported in *Pseudomonas aeruginosa*[25]

The main limitation of this study is that nursing homes are not part of CRaCKle. Rather, we are monitoring the impact of nursing homes by comprehensively monitoring all hospitalized patients with positive cultures for CRKP. Therefore, we are examining the “tip of the iceberg” and are missing those nursing home residents with rectal CRKP carriage, who are not admitted to the hospital or who have no clinical cultures positive for CRKP. Follow-up studies are needed that examine this issue directly in the nursing home. However, this multi-center consortium covers the great majority of hospitals in the region and by employing a

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comprehensive inclusion strategy, we have an unbiased cohort. In addition, these are the patients who confront acute care physicians. Another limitation of this study is that data on prior antibiotic usage was evaluated only for the 14-day period prior to the first positive CRKP culture. Only antibiotics reported either in notes or medication lists of the electronic medical record were included which may have led to an underestimation of antibiotic usage. However, in an independent cohort, tigecycline use also was the only antibacterial independently associated with tigecycline resistance[15]. This validates our finding that tigecycline use is a major driver of tigecycline resistance development. While this is intuitive, it is important to note that for other MDRO, a direct link is not always the main driver of resistance; for instance ceftriaxone use rather than vancomycin use was shown to be related to vancomycin resistance in *Enterococcus faecium*[26]. Finally, only patients with isolates that were clinically tested for tigecycline susceptibility were included, which may have resulted in an over-estimate of tigecycline non-susceptibility. However, the majority of CRKP isolates in CRACKLE are routinely tested for tigecycline susceptibility.

In summary, in this multi-center, prospective cohort of hospitalized patients with CRKP, patients with tigecycline non-susceptible isolates were found to be similar in most respects to patients with tigecycline susceptible CRKP. The three variables associated with decreased tigecycline susceptibility were previous tigecycline exposure, admission from a nursing home setting, and a positive culture for CRKP within the first 2 days of hospitalization. These findings emphasize the need for antimicrobial stewardship, as well as the urgent need for evaluation of optimal infection control practices in long term care.

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References

1. Perez F, van Duin D. Carbapenem-resistant Enterobacteriaceae: a menace to our most vulnerable patients. Cleve Clin J Med. 2013; 80:225–233. [PubMed: 23547093]
2. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis. 2013; 13:785–796. [PubMed: 23969216]
3. van Duin D, Kaye KS, Neuner EA, Bonomo RA. Carbapenem-resistant Enterobacteriaceae: a review of treatment and outcomes. Diagn Microbiol Infect Dis. 2013; 75:115–120. [PubMed: 23290507]
4. Flamm RK, Farrell DJ, Sader HS, Jones RN. Ceftazidime/avibactam activity tested against Gram-negative bacteria isolated from bloodstream, pneumonia, intra-abdominal and urinary tract infections in US medical centres (2012). J Antimicrob Chemother. 2014; 69:1589–1598. [PubMed: 24562613]
5. Walkty A, Adam H, Baxter M, et al. In Vitro Activity of Plazomicin against 5,015 Gram-Negative and Gram- Positive Clinical Isolates Obtained from Patients in Canadian Hospitals as Part of the

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CANWARD Study, 2011–2012. Antimicrob Agents Chemother. 2014; 58:2554–2563. [PubMed: 24550325]

6. Mathers AJ, Cox HL, Kitchel B, et al. Molecular dissection of an outbreak of carbapenem-resistant enterobacteriaceae reveals Intergenus KPC carbapenemase transmission through a promiscuous plasmid. MBio. 2011; 2:e00204–00211. [PubMed: 22045989]
7. Van Duin D, Cober E, Richter S, et al. Tigecycline Therapy for Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) Bacteriuria Leads to Tigecycline Resistance. Clin Microbiol Infect. 201410.1111/1469-0691.12714
8. 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; 58:4035–4041. [PubMed: 24798270]
9. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement. CLSI document M100-S24. 2014; 34
10. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007; 44(Suppl 2):S27–72. [PubMed: 17278083]
11. American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005; 171:388–416. [PubMed: 15699079]
12. Centers for Disease Control and Prevention. CDC/NHSN Surveillance Definitions for Specific Types of Infections. CDC/NHSN Surveillance Definitions for Specific Types of Infections. 2014. Available at: www.cdc.gov/nhsn
13. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. Int J Antimicrob Agents. 1999; 11:7–12. [PubMed: 10075272]
14. 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; 40:373–383. [PubMed: 3558716]
15. Nigo M, Cevallos CS, Woods K, et al. Nested case-control study of the emergence of tigecycline resistance in multidrug-resistant Klebsiella pneumoniae. Antimicrob Agents Chemother. 2013; 57:5743–5746. [PubMed: 23979745]
16. Prabaker K, Lin MY, McNally M, et al. Transfer from High-Acuity Long-Term Care Facilities Is Associated with Carriage of Klebsiella pneumoniae Carbapenemase-Producing Enterobacteriaceae: A Multihospital Study. Infect Control Hosp Epidemiol. 2012; 33:1193–1199. [PubMed: 23143355]
17. 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; 40:760–765. [PubMed: 22285709]
18. Ben-David D, Maor Y, Keller N, et al. Potential role of active surveillance in the control of a hospital-wide outbreak of carbapenem-resistant Klebsiella pneumoniae infection. Infect Control Hosp Epidemiol. 2010; 31:620–626. [PubMed: 20370465]
19. Adler A, Hussein O, Ben-David D, et al. Persistence of Klebsiella pneumoniae ST258 as the predominant clone of carbapenemase-producing Enterobacteriaceae in post-acute-care hospitals in Israel, 2008–13. J Antimicrob Chemother. 2015; 70:89–92. [PubMed: 25204343]
20. Centers for Disease Control and Prevention. 2014. p. 2014http://www.cdc.gov/longtermcare/ Accessed 11/13/2014
21. Daneman N, Gruneir A, Bronskill SE, et al. Prolonged antibiotic treatment in long-term care: role of the prescriber. JAMA internal medicine. 2013; 173:673–682. [PubMed: 23552741]
22. Daneman N, Gruneir A, Newman A, et al. Antibiotic use in long-term care facilities. J Antimicrob Chemother. 2011; 66:2856–2863. [PubMed: 21954456]
23. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococcus, gram-negative bacilli, Clostridium difficile, and Candida. Ann Intern Med. 2002; 136:834–844. [PubMed: 12044132]

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24. Tumbarello M, Viale P, Viscoli C, et al. Predictors of Mortality in Bloodstream Infections Caused by Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae: Importance of Combination Therapy. Clin Infect Dis. 2012; 55:943–950. [PubMed: 22752516]

25. Winkler ML, Papp-Wallace KM, Hujer AM, et al. Unexpected Challenges in Treating Multidrug-Resistant Gram-Negative Bacteria: Resistance to Ceftazidime-Avibactam in Archived Isolates of Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2015; 59:1020–1029. [PubMed: 25451057]

26. McKinnell JA, Kunz DF, Chamot E, et al. Association between vancomycin-resistant Enterococci bacteremia and ceftriaxone usage. Infect Control Hosp Epidemiol. 2012; 33:718–724. [PubMed: 22669234]

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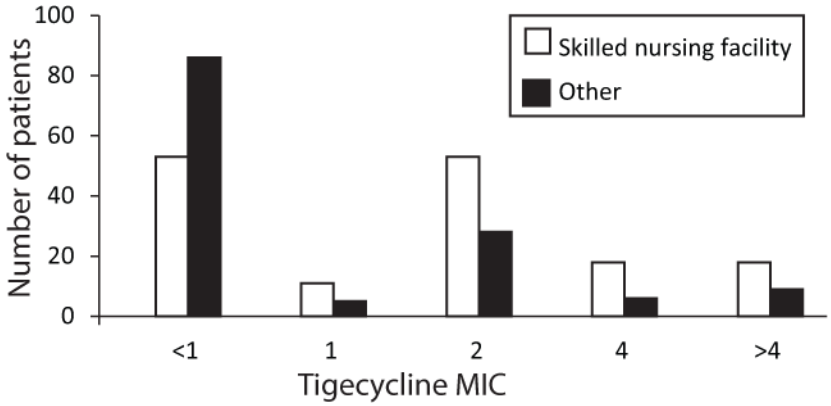

Figure 1.

Tigecycline minimal inhibitory concentration (MIC) distribution in carbapenem-resistant *Klebsiella pneumoniae* isolates by origin prior to hospitalization.

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Table 1

Demographics.

	All	Tigecycline Susceptible	Tigecycline Non-Susceptible	p
n	287	155	132	
Age, median (IQR)	71 (59–81)	69 (57–79)	72 (63–83)	0.0512
Gender, Female	181 (63)	93 (60)	88 (67)	0.2703
Race				0.6346
White	154 (54)	87 (56)	67 (51)	
Black	118 (41)	60 (39)	58 (44)	
Other	14 (5)	8 (5)	6 (5)	
Charlson comorbidity index	3 (2–5)	3 (2–5)	4 (2–6)	0.0520
Diabetes mellitus	149 (52)	73 (47)	76 (58)	0.0969
Chronic kidney disease	65 (23)	36 (23)	29 (22)	0.8876
Malignancy	37 (13)	19 (12)	18 (14)	0.7281
Immunocompromised	27 (9)	18 (12)	9 (7)	0.2234
Corticosteroids	13 (5)	5 (3)	8 (6)	–
Solid organ transplant	11 (4)	10 (6)	1 (1)	–
Hematopoietic stem cell transplant	2 (1)	2 (1)	0	–
HIV infection	1 (0)	1 (1)	0	–
Origin				<0.0001
Skilled nursing facility	153 (53)	64 (41)	89 (67)	
Home	77 (27)	49 (32)	28 (21)	
Hospital transfer	37 (13)	30 (19)	7 (5)	
Long term acute care	20 (7)	12 (8)	8 (6)	

All data in n (%), unless otherwise indicated. IQR: interquartile range

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Table 2

Culture data.

	All	Tigecycline Susceptible	Tigecycline Non-Susceptible	p
n	287	155	132	
Source				0.5238
Urine	175 (61)	91 (59)	84 (64)	
Blood	39 (14)	26 (17)	13 (10)	
Wound	33 (11)	18 (11)	15 (11)	
Respiratory	31 (11)	16 (10)	15 (11)	
Other	9 (3)	4 (3)	5 (4)	
Infection	127 (44)	74 (48)	53 (40)	0.2332
Critically ill at time of culture[a]	93 (32)	54 (35)	39 (30)	0.3767
Patient location at time of culture				0.3950
Ward	119 (41)	69 (45)	50 (38)	
Intensive care unit	91 (32)	49 (32)	42 (32)	
Emergency department	77 (27)	37 (24)	40 (30)	
Present on admission[b]	184 (64)	89 (57)	95 (72)	0.0134
Hospital length of stay, days, median (IQR)	10 (6–18)	12 (7–23)	8 (5–14)	0.0015

All data in n (%), unless otherwise indicated.

[a] as defined by Pitt bacteremia score≥4 on the day of first positive culture.

[b] defined as a positive culture within within 48 hours of hospitalization. IQR: interquartile range

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Table 3

Exposure to antibiotics in 14 days prior to first positive culture.

	All	Tigecycline Susceptible	Tigecycline Non-Susceptible	p
n	287	155	132	
Exposure to any antibiotic in 14 days prior to cultures	111 (39)	56 (36)	55 (42)	0.3947
Tigecycline	16 (6)	4 (3)	12 (9)	0.0201
Carbapenem	44 (15)	28 (18)	16 (12)	0.1899
Fluoroquinolone	53 (18)	30 (19)	23 (17)	0.7607
Colistin	3 (1)	2 (1)	1 (1)	1.000
Vancomycin	87 (30)	47 (30)	40 (30)	1.000
β-lactam/β-lactamase inhibitor	62 (22)	36 (23)	26 (20)	0.5651
Cephalosporin	27 (9)	15 (10)	12 (9)	1.000
Aminoglycoside	18 (6)	10 (6)	8 (6)	1.000
Metronidazole	13 (5)	7 (5)	6 (5)	1.000
Daptomycin	14 (5)	9 (6)	5 (4)	0.5844
Other	76 (26)	48 (31)	28 (21)	0.0807
Number of classes of antibiotics				0.6796
None	111 (39)	56 (36)	55 (42)	
One	52 (18)	28 (18)	24 (18)	
Two	58 (20)	35 (23)	24 (18)	
more than two	66 (23)	36 (23)	30 (23)	

All data in n (%), unless otherwise indicated.

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Table 4

Risk factors for tigecycline non-susceptibility.

	OR	95% CI	p
Admission from skilled nursing facility	2.52	1.51–4.24	0.0004
Present on admission	1.77	1.03–3.08	0.038
Receipt of tigecycline within 14 days	4.41	1.36–17.24	0.012

Multivariable logistic regression model which also included age, Charlson score and presence of diabetes mellitus.