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Benjamin Lee May 1st, 2021

Assessment of Non-Carbapenem Beta-Lactams in the Treatment of Patients with Urinary Tract Infections Caused by Extended Spectrum Beta-Lactamase-Producing Enterobacteriaceae

By

Benjamin Lee
Degree to be awarded: MPH

Epidemiology

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2019

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Master of Public Health
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Abstract

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By Benjamin Lee

Background: The widespread use of antibiotics has led to the development of antibiotic resistance, one of the greatest global public health threats currently. Carbapenems are the treatment of choice for patients with UTIs caused by extended-spectrum-beta-lactamase (ESBL)-producing Enterobacteriaceae. However, increased use of carbapenems is associated with the emergence of carbapenem-resistant Enterobacteriaceae.

Objective: To compare the effectiveness of non-carbapenem beta-lactam (NCBL) antibiotics with carbapenem in treating patients with a UTI caused by an ESBL-producing organism.

Materials and Methods: This was a retrospective cohort study of adult patients admitted to one of four Emory Healthcare hospitals with a diagnosis of UTI caused by an ESBL-producing organism from April 1, 2014 to April 30, 2018. The primary outcome was length of hospital stay. Secondary outcomes included discharge disposition, microbiological eradication, clinical relapse, in-hospital mortality, 30-day readmission rate, rate of *C. difficile* infection, rate of secondary infection with a new multi-drug organism, number of days to transition to oral therapy, and secondary infection with a carbapenem-resistant organism within 30 days. Regression models were built to determine which variables are predictive of improved or worsened outcomes for patients with UTIs caused by an ESBL-producing organism treated with either NCBL or carbapenem antibiotics.

Results: There were a total of 492 patients included in the analysis (321 patients received carbapenems and 171 received NCBLs). Use of carbapenems was not predictive of shorter hospital stay (OR: 0.99, CI: 0.98-1.00) or lower mortality rate (OR: 1.00, CI: 0.94-1.06) when compared with NCBL antibiotics in our multivariant analysis. However, it was associated with a higher likelihood of clinical relapse (OR: 1.08, CI: 1.02-1.14) and failure to eradicate microorganisms in culture samples (OR: 1.05, CI: 1.01-1.10).

Conclusions: Treatment of UTI patients caused by ESBL producers with NCBL antibiotics result in similar mortality and length of hospital stay when compared to treatment with carbapenems. NCBL antibiotics appear to be an alternative to carbapenems in treating those patients; however differences in intermediate outcomes (e.g., disease relapse, microorganism eradication) need further study to understand their clinical importance.

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Background:

Since the discovery of penicillin by Alexander Fleming almost a century ago, many different classes of antibiotics have been developed to treat patients with bacterial infections. This has greatly reduced the number of deaths associated with bacterial infections and improved patient clinical outcomes. The widespread use of antibiotics, however, has also resulted in development of antibiotic resistance, the ability of bacteria to resist killing or growth inhibition by an antibiotic or a combination of multiple different antibiotics. The emergence of antibiotic resistance is one of the greatest global public health threats currently as more than 2.8 million antibiotic-resistant infections occur in the U.S. each year and more than 35,000 patients die from them[1]. Leading examples of antibiotic-resistant bacteria include methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile* (C. difficile), and multi-drug resistant *Enterobacteriaceae*.

Enterobacteriaceae are a large family of Gram-negative bacteria that frequently cause infections in healthcare settings and in communities[2]. *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae (K. pneumoniae)* are the two most common organisms causing urinary tract infection (UTI)[3]. Antibiotics such as ampicillin and trimethoprim are often recommended to treat patients with UTI. Multi-drug resistant *Enterobacteriaceae* have emerged as a problem because there are fewer antibiotic options for treating infections caused by these organisms. Some multi-drug resistant *Enterobacteriaceae* produce enzymes called extended-spectrum-beta-lactamases (ESBLs) which can break down and destroy commonly used antibiotics such as

penicillins and cephalosporins[2]. Providers treating patient with UTIs caused by ESBL-producing *Enterobacteriaceae* often prescribe the traditional drug of last resort, the antibiotics in the class carbapenems, such as meropenem[4,5]. However, the increased use of carbapenems is associated with the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE)[6]. CRE is listed as one of several urgent threats in the 2019 CDC Antibiotic Resistance Threats Report[1], as CRE is often resistant to all available antibiotics and difficult to eradicate[7]. Another reason why CRE is listed as urgent is that CRE can share a mobile genetic element with other bacteria which rapidly spread resistance to carbapenem antibiotics[1]. In addition, CRE is responsible for up to half of the mortality in patients with bloodstream infections from them[8].

To minimize the unnecessary use of carbapenems and reduce the emergence of CRE, there have been a few studies that examined carbapenem-sparing antibiotic regimens for treating infections caused by ESBL producers. One such regimen is beta-lactam/beta-lactamase inhibitor (BLBLI) antibiotics combination such as piperacillin-tazobactam, which ESBL-producing bacteria are frequently susceptible to. Some preliminary observational studies have suggested that these carbapenem-sparing regimens such as piperacillin-tazobactam and ceftolozane-tazobactam may be clinically effective for treating infections caused by ESBL-producing Enterobacteriacea[9]; however some contradictory results have been reported in terms of outcomes in patients receiving a BLBLI versus a carbapenem regimen[10]. Some observational studies showed no significant difference in mortality while other studies showed higher mortality rates in patients receiving a BLBLI regimen compared with those receiving a carbapenem regimen[11,12].

One important study aimed at resolving the discrepancies from the prior studies and building evidence that carbapenem-sparing regimens have similar clinical efficacy as carbapenem regimens was the MERINO trial[13]. In this noninferiority, parallel group, randomized clinical trial, Harris and colleagues examined the difference in mortality among patients treated with piperacillin-tazobactam versus one specific carbapenem, meropenem, for bloodstream infections caused by ceftriaxone-resistant *E.coli* or *K. pneumoniae*. The trial was terminated early because there was a higher mortality rate within the piperacillin-tazobactam group compared to the meropenem group after reviewing data of the initially enrolled patients[13].

Introduction:

It remains unclear from the MERINO trial, however, whether BLBLI agents would be as effective as carbapenems to treat UTI caused by ESBL producers in patients with low mortality risk or without a bloodstream infection. Because UTIs are more common and less severe than bloodstream infections[14,15], it is hypothesized that carbapenem-sparing regimen might achieve the same clinical outcomes as carbapenems in treating simple UTIs caused by ESBL producers. To test this hypothesis, we performed a retrospective analysis of hospital patients with UTI caused by ESBL-producing organisms who were treated with either a carbapenem or a non-carbapenem β-lactam antibiotic.

Materials and Methods:

Study population, case definition, and case ascertainment:

We constructed a retrospective cohort of adult patients admitted to one of the four Emory Healthcare hospitals with a diagnosis of UTI caused by an ESBL-producing organism from April 1, 2014 to April 30, 2018. Cases were identified through chart review from positive urine culture data, and remaining information about patients was retrieved from the Emory Healthcare Clinical Data Warehouse. Patients were categorized as being treated with either a non-carbapenem beta-lactam (NCBL) or a carbapenem antibiotic.

Patient demographics included age, weight, and sex. Comorbidities and characteristics of the UTI patients included use of antineoplastics, active corticosteroid use of 30 mg/day of prednisone or equivalent dose, presence of a solid organ or hematologic malignancy, infection with HIV with a CD4 cell count of <200 cells/mL, diabetes, neutrophil count < 500 cells/mcL, use of an immunosuppressive agent, presence of a urinary catheter, type of organism causing the UTI, and bacteremic status. Patients were considered to have a complicated UTI if they had one or more of these comorbidities and characteristics.

The primary outcome was length of hospital stay. Secondary outcomes included discharge disposition (defined as positive for death or hospice care, negative if discharged to skilled nursing facility or home), microorganism eradication (defined as positive if repeat urine cultures

were negative, negative if repeat urine cultures were positive, and uncertain if no repeat urine cultures were collected), and clinical relapse.

Additional secondary outcomes that were not modeled included clinical response to therapy (defined as positive if there was documented improvement in symptoms, negative if there was documented treatment failure, or uncertain if there were no comments on resolution of symptoms), in-hospital mortality, 30-day readmission rate, days to transition from intravenous (IV) to per oral (PO) therapy, total days of therapy, rates of *Clostridioidies difficile* infection within eight weeks, rates of secondary infection with a new multi-drug resistant (MDR) organism at a site other than urine (defined as resistance to at least one agent from three different classes of antibiotics), and secondary infection with a carbapenem-resistant organism at any site within 30 days.

Statistical analysis:

We conducted a descriptive analysis to compare patients who had received carbapenem antibiotics with patients who had received NCBL antibiotics in order to determine any differences between the two groups. Statistical significance was tested using chi-square tests for the categorical variables and student's t-tests on continuous variables. Histograms of length of hospital stay were created to determine the appropriate distribution assumption to use for modeling.

We created a correlation matrix to evaluate collinearity and to determine which variables were collinear for the purpose of statistical modeling. Any variables with more than two correlations > 0.25 were not eligible to be present in the same model. CD4 cell count <200 was also excluded due to the low number of patients positive for this factor.

We constructed logistic regression models with binomial distributions to determine what variables or characteristics would predict each categorical outcome best. These outcomes included death or hospice placement, positive microorganism eradication, and clinical relapse. For the outcome of length of hospital stay, we used a generalized linear model with an inverse-Gaussian distribution to account for the non-normal distribution of the outcome. Eligible predictors for the models included age, weight, sex, use of antineoplastics, diabetes, use of urinary catheter, use of immunosuppressive agents, and bacteremic status. Patients who were listed as unknown for positive microorganism eradication were categorized as successes for the purpose of modeling. Patients who had a malignancy or had a length of stay greater than 100 days were excluded from the model for length of hospital stay. After constructing base models, organism type (*E. coli* vs other) and whether the patient received a carbapenem antibiotic or a NCBL antibiotic were added in individually and jointly to examine the influence of organism and/or use of carbapenem antibiotic on the outcome.

All analyses were conducted in RStudio version 4.0.2. A p value of less than 0.05 is considered significant.

Results:

Descriptive analysis results:

A total of 492 patients were included in this retrospective cohort. The median age of the patients was 70 (IQR: 57-81) with a median weight of 73kg (IQR: 63.7-92). The majority of patients were female (72%). Among the 492 patients, 321 (65.2%) were treated with a carbapenem antibiotic and 171 (34.8%) were treated with an NCBL antibiotic (Table 1). There were 10 different NCBL agents used and 3 different carbapenem agents used across the study population (Supplemental Table 1).

As shown in Table 1, the two groups of patients (those treated with a carbapenem and those treated with an NCBL) were of similar age, weight, and sex proportion. There were a higher percentage of bacteremic patients in the carbapenem group (37, 11.5%) than the NCBL group (4, 2.3%) ($p<0.01$). The percentage of those who had *E.coli* as the causative organism was higher in the carbapenem group (249, 77.6%) than the NCBL group (86, 50.3%) ($p<0.01$). The use of immunosuppressive agents was also higher in percentage in the carbapenem group than the NCBL group (14.6% vs 3.5%) ($p<0.01$).

There was a significant difference in number of days to transition to PO therapy and duration of treatment between the carbapenem group and the NCBL group (median 9 vs 4 days, $p<0.01$; median 10 vs 7 days, $p<0.01$). There was also a significant difference in disease relapse rate and microorganism eradication between the two groups ($p<0.01$ for both). There is no statistically

significant difference in hospital mortality. Although the length of hospital stay is slightly longer in the carbapenem group than the NCBL group (median 8 vs 7 days, p=0.03) (Table 1, Figures 1-2), this difference is not statistically significant in our multivariant analysis.

Modeling results:

We first created a correlation matrix of all the available patient characteristics (Figure 3). Variables excluded due to having more than two correlations > 0.25 were corticosteroid use, malignancy, absolute neutrophils, and complicated UTI. CD4 cell count <200 was also excluded due to the low number of patients positive for this factor. We then analyzed several patient outcomes and the characteristics that predict these outcomes. These include 1) death or hospice placement, 2) clinical relapse, 3) failure to eradicate microorganism in culture sample, and 4) length of hospital stay.

Among all patients included for modeling the outcome of death or hospice placement (n=492), significant predictors included bacteremic status (OR: 0.90, CI: 0.81-1.00; p=0.05), diabetes (OR: 0.94, CI: 0.89-1.00; p=0.04), use of antineoplastic drugs (OR: 1.07, CI: 1.00-1.14; p=0.04), and use of catheter (OR: 1.10, CI: 1.04-1.16; p<0.01) (Table 2). When limiting the model to only those with negative bacteremic status (n=451), use of antineoplastic drugs (OR: 1.07, CI: 1.00-1.15; p=0.04) and use of catheter (OR: 1.11, CI: 1.04-1.18; p<0.01) remains the best at predicting the outcome. Diabetes and the type of organism (OR: 0.96, CI: 0.90-1.02) no longer impact the prediction of this outcome. Regardless of the bacteremic status, the type of

antibiotics used was not predictive of this outcome (OR: 1.00, CI: 0.94-1.06; p>0.05; Tables 2 and 2a).

Among all patients included for modeling the outcome of clinical relapse (n=492), significant predictors included use of immunosuppressive agent (OR: 1.17, CI: 1.08-1.27; p<0.01) and use of carbapenem (OR: 1.08, CI: 1.02-1.14). Limiting the model to only those with negative bacteremic status (n=451), use of immunosuppressive agent (OR: 1.14, CI: 1.05-1.25; p<0.01) use of carbapenem (OR: 1.10, CI: 1.04-1.16; p<0.01) were still the best at predicting the outcome. Regardless of the bacteremic status, the use of immunosuppressive agent and treatment with a carbapenem are associated with a higher likelihood of clinical relapse (Tables 3 and 3a; p<0.01 for both).

Among all patients included for modeling the outcome of failure to eradicate microorganism in culture sample (n=491), significant predictors included sex (OR: 1.05, CI: 1.01-1.10; p=0.02) and use of immunosuppressive agent (OR: 1.17, CI: 1.09-1.25; p<0.01). Treatment with a carbapenem was associated with a higher likelihood of failure to eradicate microorganism (OR: 1.05, CI: 1.01-1.10; p=0.02). Including type of organism to this model does not significantly impact the prediction of this outcome (OR: 1.01, CI: 0.97-1.05; p=0.81). When limiting the model to only those with negative bacteremic status (n=451), the association between carbapenem and failure to eradicate microorganism persisted (OR: 1.10, CI: 1.04-1.17), so were sex and the use of immunosuppressive agent (p<0.01 for both) (Tables 4 and 4a).

Among all patients included for modeling the outcome of length of hospital stay (n=348), significant predictors included age (OR: 1.00, CI: 1.00-1.00; p<0.01), weight (OR: 1.00, CI: 1.00-1.00; p<0.01), and use of antineoplastic drugs (OR: 0.97, CI: 0.95-0.98; p<0.01). When including organism type into the model, organism type correlates with higher likelihood of longer hospital stay (OR: 1.04, CI: 1.02-1.06; p<0.01). Including carbapenem into the model has no significant impact on predicting length of hospital stay (OR: 0.99, CI: 0.98-1.00; p=0.29) (Table 5).

Discussion:

In this retrospective study, we found that patients with UTIs caused by ESBL-producing organisms treated with NCBLs had on average fewer days to transition to PO therapy and shorter duration of therapy compared to patients treated with carbapenems. However, patients had similar lengths of hospitalization regardless of being treated with carbapenems or NCBLs. For the outcomes of death or hospice placement, clinical relapse, and positive microorganism eradication, there were a significantly difference in the percentage of patients who were treated with carbapenems than that of patients who were treated with NCBLs. The type of organism responsible for the UTI in patients was also significantly different between the carbapenem and the NCBL groups (Table 1).

The models for predicting death or hospice placement show that carbapenems are not better than NCBLs (Table 2). Likewise, models showed that treatment with carbapenems was not predictive of shorter hospital stay (Table 5). However, the models for disease relapse did show that treatment with carbapenem was predictive of relapse with about a 1.08 times higher likelihood of relapse if a patient was to receive a carbapenem antibiotic instead of an NCBL antibiotic (Table 3). This correlates with there being a greater proportion of relapsed patients within the carbapenem group than the NCBL group (Table 1). Models for predicting failure to eradicate microorganisms in culture samples show that treatment with carbapenem had about a 1.05 times higher likelihood of failing to eradicate in culture samples if a patient was to receive a carbapenem antibiotic instead of an NCBL antibiotic (Table 4). These findings do not

necessarily indicate that use of carbapenems is worse than use of NCBLs for preventing relapse of UTI and/or eradicating microorganisms in culture samples. Carbapenems are most often used for higher risk and harder to treat infections caused by ESBL-producing organisms. This could explain why there seems to be more relapsed patients within the carbapenem group, as patients from the carbapenem group are likely to have more comorbidities and/or severe infections than patients from the NCBL group.

Our results show that NCBL antibiotics are as effective as carbapenems for the treatment of patients with UTIs caused by an ESBL-producing organism regarding mortality and length of hospital stay in our multivariant analysis of this retrospective cohort. These findings are in agreement with those reported in some previous studies. However, some studies found that non-carbapenem regimens are less efficacious than carbapenem regimens[11]. In contrast, our study found that non-carbapenem beta-lactams appear to more efficacious to eradicate microorganisms and are less disease relapse. There are multiple factors that could explain this discrepancy, including different patient study populations and outcomes. Many of the existing literature focuses on patients with bloodstream infections rather than patients with UTIs. Outcome often examined was mortality and this study examined length of hospital stay, clinical relapse, and failure to eradicate microorganism culture samples in addition to mortality.

This study does have some limitations. The biggest limitation is that patients who were treated with carbapenems may be clinically different from those treated with NCBLs. These patients may be more likely to relapse and/or fail to clear the microorganisms. It was surprising to see

that there were worse outcomes for being treated with carbapenems as carbapenems are the drug of last resort. Uncontrolled variables such as underlying illness may have confounded the results. Our modeling was able to account for some differences in underlying illness by including some variables associated with complicated UTI. However, the data is incomplete to conclude whether carbapenems are actually associated with more disease relapse or failure to eradicate microorganisms or if these worse outcomes are due to more severe underlying illnesses within the carbapenem group. For future studies, more data regarding patient status would be collected to control for these confounding factors.

Conclusions:

In this retrospective cohort study using descriptive and generated statistical models, we showed that patients with UTIs caused by ESBL-producing *Enterobacteriaceae* treated with NCBL antibiotics have similar mortality and length of hospital stay with those treated with carbapenems. NCBL antibiotics appear to be an adequate substitute for carbapenems in treating those patients; however differences in intermediate outcomes (e.g., disease relapse, microorganism eradication) need further study to understand their clinical importance.

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Figures and Tables:

Figure 1: Histogram of length of hospital stay for patients treated with a carbapenem antibiotic

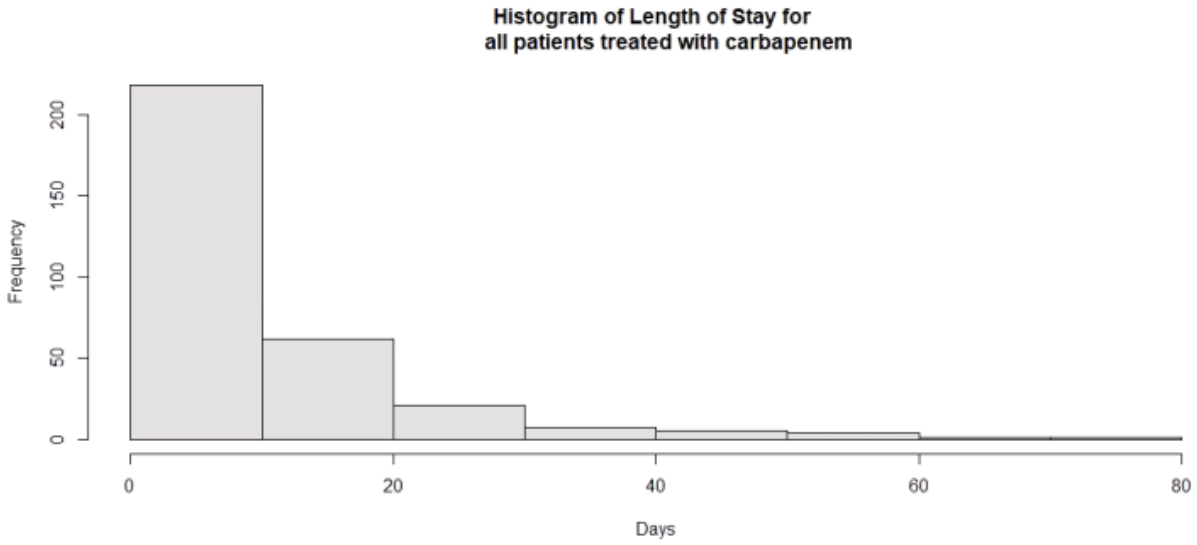

Figure 2: Histogram of length of hospital stay for patients treated with a NCBL antibiotic

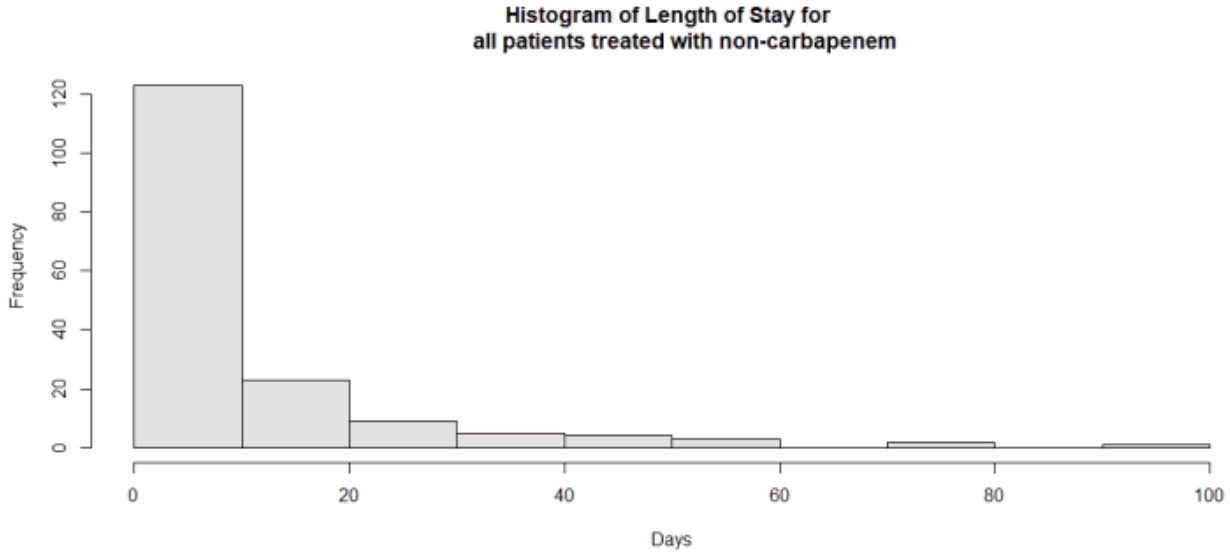

Figure 3: Correlation matrix among the patient's characteristics

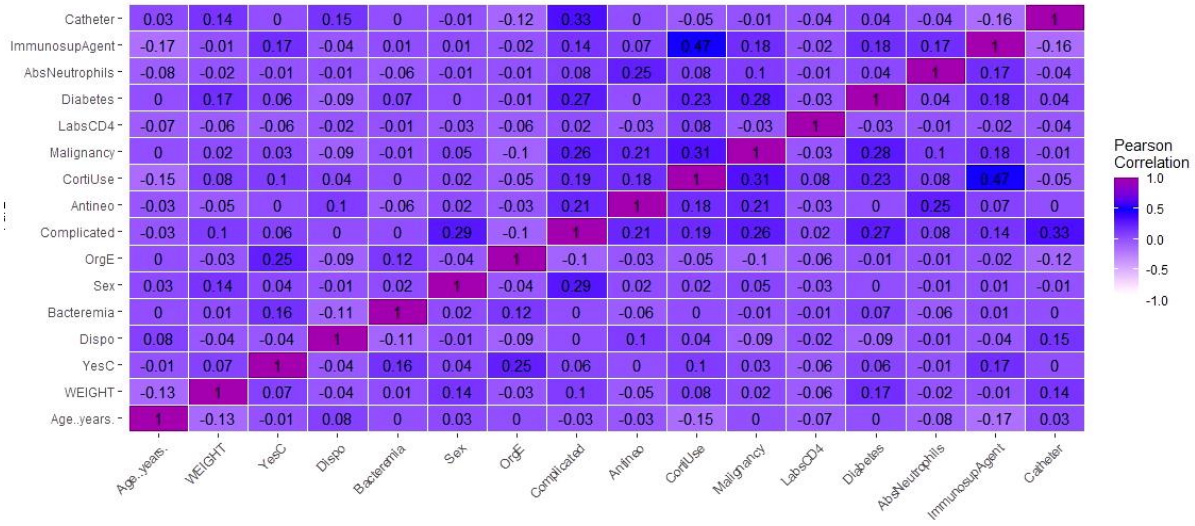

Table 1: Summary of patient data between carbapenem and non-carbapenem groups			
Characteristics	***Carbapenem (n=321) Median (q1-q3) /Frequency (%)***	***Non-carbapenem (n=171) Median (q1-q3)/Frequency (%)***	***P-value***
Age	69 (56-81)	72 (59-81)	0.57
Weight	75.4 (63.8-94)	70 (63.6-89.65)	0.14
Male (%)	111 (34.58%)	52 (30.41%)	0.40
Outcomes			
Length of hospital stay	8 (5-13)	7 (4-12)	0.03
Days to PO* therapy	9 (6-14)	4 (3-6)	<0.01
DOT	10 (7-14)	7 (5-10)	<0.01
Positive Micro Eradication			
Yes	118 (36.76%)	51 (29.82%)	<0.01
No	26 (8.1%)	2 (1.17%)	
Unknown	177 (55.14%)	118 (69.01%)	
Relapsed (%)	42 (13.08%)	5 (2.92%)	<0.01
Secondary MDR	29 (9.03%)	9 (5.26%)	0.19
Secondary CRE	2 (0.62%)	0 (0%)	NA
Positive Clinical Response			
Yes	149 (46.42%)	90 (52.63%)	0.38
No	14 (4.36%)	4 (2.34%)	
Unknown	158 (49.22%)	77 (45.03%)	
30 day readmission (%)	154 (47.98%)	77 (45.03%)	0.60
In hospital mortality (%)	12 (3.74%)	7 (4.09%)	0.81
Disposition location			
Home	65 (20.25%)	55 (32.16%)	0.01
Hospice	22 (6.85%)	16 (9.36%)	<0.01
SNF	222 (69.16%)	93 (54.39%)	0.42
Other	12 (3.74%)	7 (4.09%)	<0.01
C. diff			
Yes	18 (5.61%)	6 (3.51%)	0.43
No	226 (70.4%)	117 (68.42%)	
Unknown	77 (23.99%)	48 (28.07%)	
Factors			
Bacteremia (%)	37 (11.53%)	4 (2.34%)	<0.01
Complicated UTI (%)			
Yes	280 (87.23%)	141 (82.46%)	0.19
No	18 (5.61%)	14 (8.19%)	
Missing	23 (7.17%)	16 (9.36%)	
Antineoplastics			
Yes	81 (25.23%)	43 (25.15%)	1
No	163 (50.78%	80 (46.78%)	
Missing	77 (23.99%)	48 (28.07%)	
Corticosteroid Use			
Yes	89 (27.73%)	32 (18.71%)	0.05
No	155 (48.29%)	91 (53.22%)	
Missing	77 (23.99%)	48 (28.07%)	

Malignancy			
Yes	97 (30.22%)	46 (26.9%)	0.50
No	147 (45.79%)	77 (45.03%)	
Missing	77 (23.99%)	48 (28.07%)	
CD4 count <200			
Yes	0 (0%)	1 (0.58%)	0.35
No	244 (76.01%)	122 (71.35%)	
Missing	77 (23.99%)	48 (28.07%)	
Diabetes			
Yes	112 (34.89%)	49 (28.65%)	0.32
No	132 (41.12%)	74 (43.27%	
Missing	77 (23.99%)	48 (28.07%)	
Absolute neutrophils			
Yes	12 (3.74%)	7 (4.09%)	0.81
No	232 (72.27%)	116 (67.84%)	
Missing	77 (23.99%)	48 (28.07%)	
Immunosuppressive agent			
Yes	47 (14.64%)	6 (3.51%)	<0.01
No	197 (61.37%)	117 (68.42%)	
Missing	77 (23.99%)	48 (28.07%)	
Catheter			
Yes	131 (40.81%)	70 (40.94%)	1
No	190 (59.19%)	101 (59.06%)	
Missing	0 (0%)	0 (0%)	
Type of organism			
E. coli	249 (77.57%)	86 (50.29%)	<0.01
K. pneumoniae	63 (19.63%)	39 (22.81%)	
Cloacae	10 (3.12%)	22 (12.87%)	
Other	8 (2.49%)	24 (14.04%)	

*PO, per oral; DOT, duration of treatment; micro, microorganism; MDR, multi-drug resistance; CRE, carbapenem-resistant *Enterobacteriae*; SNF, skilled nursing facility

Table 2: Regression models with hospice/death as an outcome

Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Bacteremia	0.89 (0.03)	0.90 (0.03)	0.90 (0.04)	0.90 (0.05)
Age	1.00 (0.07)	1.00 (0.07)	1.00 (0.07)	1.00 (0.07)
Diabetes	0.94 (0.04)	0.94 (0.05)	0.94 (0.04)	0.94 (0.04)
Antineoplastic	1.07 (<0.01)	1.07 (0.03)	1.07 (0.04)	1.07 (0.04)
Catheter	1.10 (<0.01)	1.10 (<0.01)	1.10 (<0.01)	1.10 (<0.01)
Carbapenem	NA	0.99 (0.63)	NA	0.99 (0.20)
Organism (*E.coli*)	NA	NA	0.96 (0.17)	0.96 (0.87)
Model Statistics				
AIC value	257.54	261.85	260.18	262.16
R^2 value	0.05	0.05	0.05	0.05

[1] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter$

[2] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter + \beta_6 Carbapenem$

[3] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter + \beta_6 Ecoli$

[4] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter + \beta_6 Carbapenem + \beta_7 Ecoli$

Table 2a: Regression models with hospice/death as an outcome excluding bacteremic patients

Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Age	1.00 (0.07)	1.00 (0.07)	1.00 (0.07)	1.00 (0.07)
Antineoplastics	1.08 (0.04)	1.08(0.04)	1.07 (0.04)	1.07 (0.04)
Diabetes	0.94 (0.05)	0.94 (0.06)	0.94 (0.05)	0.94 (0.06)
Catheter	1.11 (<0.01)	1.11 (<0.01)	1.11 (<0.01)	1.11 (<0.01)
Carbapenem	NA	0.99 (0.64)	NA	1.00 (0.88)
Organism (*E.coli*)	NA	NA	0.96 (0.18)	0.96 (0.21)
Model Statistics				
AIC value	275.17	276.94	275.35	277.33
R^2 value	0.04	0.04	0.04	0.04

[1] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter$

[2] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter + \beta_6 Carbapenem$

[3] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter + \beta_6 Ecoli$

[4] - $Y = \alpha + \beta_1 Bacteremia + \beta_2 Age + \beta_3 Diabetes + \beta_4 Antineoplastics + \beta_5 Catheter + \beta_6 Carbapenem + \beta_7 Ecoli$

Table 3: Regression models with relapse as an outcome				
Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Sex	1.05 (0.08)	1.05 (0.10)	1.05 (0.07)	1.05 (0.09)
Immunosuppressive agent	1.19 (<0.01)	1.17 (<0.01)	1.20 (<0.01)	1.17 (<0.01)
Catheter	0.95 (0.06)	0.95 (0.04)	0.96 (0.09)	0.95 (0.06)
Carbapenem	NA	1.09 (<0.01)	NA	1.08 (<0.01)
Organism (*E.coli*)	NA	NA	1.043 (0.13)	1.02 (0.43)
Model Statistics				
AIC value	174.65	167.58	174.29	168.95
R^2 value	0.05	0.06	0.05	0.06

[1] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Catheter$

[2] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Catheter + \beta_4 Carbapenem$

[3] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Catheter + \beta_4 Ecoli$

[4] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Catheter + \beta_4 Carbapenem + \beta_5 Ecoli$

Table 3a: Regression models with relapse as an outcome excluding bacteremic patients				
Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Immunosuppressive agent	1.17 (<0.01)	1.14 (<0.01)	1.18 (<0.01)	1.14 (<0.01)
Catheter	0.95 (0.06)	0.95 (0.04)	0.95 (0.08)	0.95 (0.06)
Carbapenem	NA	1.10 (<0.01)	NA	1.10 (<0.01)
Organism (*E.coli*)	NA	NA	1.048 (0.10)	1.02 (0.42)
Model Statistics				
AIC value	163.88	153.87	163.1	155.21
R^2 value	0.04	0.06	0.04	0.06

[1] - $Y = \alpha + \beta_1 Immunosuppresive\_agent + \beta_2 Catheter$

[2] - $Y = \alpha + \beta_1 Immunosuppresive\_agent + \beta_2 Catheter + \beta_3 Carbapenem$

[3] - $Y = \alpha + \beta_1 Immunosuppresive\_agent + \beta_2 Catheter + \beta_3 Ecoli$

[4] - $Y = \alpha + \beta_1 Immunosuppresive\_agent + \beta_2 Catheter + \beta_3 Carbapenem + \beta_4 Ecoli$

Table 4: Regression models with failure to eradicate microorganisms in culture sample as an outcome				
Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Sex	1.05 (0.02)	1.05 (0.02)	1.05 (0.02)	1.05 (0.02)
Immunosuppressive agent	1.18 (<0.01)	1.17 (<0.01)	1.18 (<0.01)	1.17 (<0.01)
Carbapenem	NA	1.05 (0.02)	NA	1.05 (0.02)
Organism (*E.coli*)	NA	NA	1.01 (0.72)	1.00 (0.81)
Model statistics				
AIC value	-66.36	-69.75	-64.49	-67.80
R^2 value	0.06	0.07	0.06	0.06

[1] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent$
[2] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Carbapenem$
[3] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Ecoli$
[4] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Carbapenem + \beta_4 Ecoli$

Table 4a: Regression models with failure to eradicate microorganism in culture sample as an outcome excluding bacteremic patients				
Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Sex	1.06 (<0.01)	1.06 (<0.01)	1.07 (<0.01)	1.06 (<0.01)
Immunosuppressive agent	1.18 (<0.01)	1.16 (<0.01)	1.18 (<0.01)	1.16 (<0.01)
Carbapenem	NA	1.05 (0.02)	NA	1.05 (0.02)
Organism (*E.coli*)	NA	NA	1.01 (0.52)	1.00 (0.96)
Model statistics				
AIC value	-56.49	-60.10	-54.91	-58.10
R^2 value	0.06	0.07	0.06	0.07

[1] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent$
[2] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Carbapenem$
[3] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Ecoli$
[4] - $Y = \alpha + \beta_1 Sex + \beta_2 Immunosuppresive\_agent + \beta_3 Carbapenem + \beta_4 Ecoli$

Table 5: Inverse Gaussian regression models with length of hospital stay as an outcome (excluding patients diagnosed as having a malignancy and length of stay over 100 days)

Variable	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
Age	*1.00 (<0.01)*	1.00 *(<0.01)*	1.00 *(<0.01)*	1.00 *(<0.01)*
Weight	1.00 (<0.01)	1.00 *(<0.01)*	1.00 *(<0.01)*	1.00 *(<0.01)*
Antineoplastics	0.96 (<0.01)	0.97 *(<0.01)*	0.97 *(<0.01)*	0.98 *(<0.01)*
Diabetes	1.02 (0.03)	1.02 (0.03)	1.00 (0.61)	1.00 (0.70)
Carbapenem	NA	0.99 (0.23)	NA	0.99 (0.29)
Organism (E.coli)	NA	NA	1.04 (<0.01)	1.04 (<0.01)
Model statistics				
AIC value	2630.7	2630.6	2601.6	2602.2
R^2 value	0.11	0.11	0.18	0.19

[1] - $Y = \alpha + \beta_1 Age + \beta_2 Weight + \beta_3 Antineoplastics + \beta_4 Diabetes$

[2] - $Y = \alpha + \beta_1 Age + \beta_2 Weight + \beta_3 Antineoplastics + \beta_4 Diabetes + \beta_5 Carbapenem$

[3] - $Y = \alpha + \beta_1 Age + \beta_2 Weight + \beta_3 Antineoplastics + \beta_4 Diabetes + \beta_5 Ecoli$

[4] - $Y = \alpha + \beta_1 Age + \beta_2 Weight + \beta_3 Antineoplastics + \beta_4 Diabetes + \beta_5 Carbapenem + \beta_6 Ecoli$

Supplemental Table 1: List of drugs used in the two patient groups		
Agent used	Non-carbapenem group drugs (n=171)	Carbapenem group drugs (n=321)
Amoxicillin/Clavulanate	*2*	NA
Ampicillin/Sulbactam	1	NA
Aztreonam	2	NA
Cefazolin	1	NA
Cefepime	17	NA
Cefoxitin	3	NA
Ceftazidime	12	NA
Ceftriaxone	86	NA
Cephalexin	1	NA
Piperacillin/Tazobactam	46	NA
Doripenem	NA	12
Ertapenem	NA	98
Meropenem	NA	211
Distribution of agents used		