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**Risk Factors and trends associated with Bactrim non-susceptibility among patients with Carbapenem-resistant *Acinetobacter baumannii* identified through the Emerging Infections Program, 2012 to 2019**

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Master of Public Health

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By

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Bachelor of Science

Texas A&M University

2019

Thesis Committee Chair: Scott Fridkin, MD

An abstract of

A thesis submitted to the Faculty of the

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**Abstract**

Risk Factors and trends associated with Bactrim non-susceptibility among patients with Carbapenem-resistant *Acinetobacter baumannii* identified through the Emerging Infections Program, 2012 to 2019

By Clayton Carmon

Antibiotic-resistant bacteria have been identified as a serious threat to public health and can lead to high morbidity, mortality, and healthcare costs. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has been a pathogen of concern causing nosocomial infections since the early 1990s. The purpose of this study was to use surveillance data to identify potential risk factors for Bactrim non-susceptibility among CRAB isolates and to identify trends in Bactrim non-susceptibility from 2012-2019. Logistic regression modeling was used to determine the association between independent risk factors and Bactrim non-susceptibility among 1,134 CRAB cases identified through active laboratory-based surveillance between 2012 and 2019. A set of clinical risk factors were identified through literature review and assessed for statistically significant association with Bactrim non-susceptibility. Each risk factor was assessed independently in multivariable models that accounted for potential confounders. Odds ratios and respective 95% confidence intervals were calculated to determine the direction and strength of each risk factor. The final models identified significant associations between several risk factors and Bactrim non-susceptibility: Charleson Score of ≥4 versus ≤1 (OR 0.63, 95% CI 0.45, 0.88), Charleson Score 2 to 3 versus ≤1 (OR 0.70, 95% CI 0.51, 0.95), and pneumonia versus urinary tract infection (UTI) (OR 2.11, 95% CI 1.10, 4.02). The second model used to assess trends in Bactrim non-susceptibility showed that there was a slight increase in the odds of non-susceptibility to Bactrim among patients with CRAB, year over year; however, our model did not show a statistically significant increase during the study period: per one-year increase from 2012-2019 (OR 1.02, 95% CI 0.96, 1.08). Data from this study demonstrated that active surveillance could help elucidate relationships between risk factors and specific antimicrobial resistance among pathogens of concern, as well as potentially identify trends in non-susceptibility over time.

# Risk Factors and trends associated with Bactrim non-susceptibility among patients with Carbapenem-resistant *Acinetobacter baumannii* identified through the Emerging Infections Program, 2012 to 2019

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TABLE OF CONTENTS

Chapter I: Background……1

Chapter II: Manuscript

Abstract……5

Introduction……6

Methods……7

Results……11

Discussion……13

References……18

Tables……20

**LIST OF TABLES**

Table 1a: Demographics and underlying conditions of case-patients identified through Multi-Site Gram Negative Surveillance Initiative overall and by Carbapenem-resistant *Acinetobacter baumannii* isolate susceptibility to Bactrim

Table 1b: Characteristics of infection outcome among case patients and the relative risk of outcome among case-patients with carbapenem-resistant *Acinetobacter baumannii* isolates that are non-susceptible to Bactrim

Table 2: Patient, temporal, and geographic characteristics of case-patients potentially associated with Bactrim non-susceptibility or other potential predictors of non-susceptibility

Table 3: Crude and adjusted odds ratio estimates of clinical factors associated with Bactrim non-susceptibility among carbapenem-resistant *Acinetobacter baumannii* case isolates from 2012-2019

Table 4: Time trends in Bactrim non-susceptibility among carbapenem-resistant *Acinetobacter baumannii* cases

Table 5: Count and Percent of Bactrim non-susceptible Carbapenem-resistant *Acinetobacter baumannii* cases by year

## CHAPTER I: BACKGROUND

Identifying trends in antimicrobial resistance and risk factors associated with resistance in pathogens of concern, especially those affecting healthcare settings, can inform and direct infection control measures and can elucidate the effects over time of those efforts. Pathogens of concern include those in the *Acinetobacter* genus, specifically *A. baumannii* and others in the *Acinetobacter* genus, henceforth: *A. baumannii* complex, in part due to the rise in the incidence of nosocomial infections attributable to *A. baumannii* complex, but also due to the rise in antibiotic resistance among these, and other, gram-negative pathogens ("Multi-Site Gram-negative Surveillance Initiative,"). It is important to note that both incidence of infection with *A.baumannii* complex and antibiotic resistance among *A. baumannii* complex can vary drastically within nations and globally (Wong et al., 2017). Risk factors associated with antimicrobial resistance in *A. baumannnii* complex typically point to recent or concurrent healthcare exposures("Multi-Site Gram-negative Surveillance Initiative,"). These exposures include hospitalization, residence in a long-term care facility (LTCF), and having indwelling devices (Bassetti, Carnelutti, & Peghin, 2017). For *A. baumannii* specifically, patients who typically become infected with resistant *A. baumannii* complex receive intensive care in acute care hospitals; however, some reports document persistence and spread in LTCFs (Bedenić et al., 2015; Chen et al., 2018). Further risk factors pertaining to antimicrobial resistance in *A. baumannii* include age over 70 years, presence of a urinary catheter, diabetes mellitus, higher severity of illness scores, presence of a central venous catheter (CVC), current or prior intensive care unit (ICU) admission, previous colonization with *A. baumannii,* and previous healthcare exposure (Bassetti et al., 2017; Wieland, Chhatwal, & Vonberg, 2018).

As early as 1990, *Acinetobacter baumannii* was identified as a rising problem within healthcare facilities, as documented by several published outbreaks in the healthcare setting (Peleg, Seifert, & Paterson, 2008; Wieland et al., 2018). The general trend throughout the 1990s and early 2000s was one of increasing resistance rates and rates of nosocomial infections caused by resistant strains of *A. baumannii.* In fact, by 2007, *A. baumannii* was the 9th most common cause of device-associated and surgical site infections (SSI) in facilities that reported to the National Healthcare Safety Network (NHSH) with 30% of those isolates resistant to carbapenems, and by 2010 that percentage of resistant isolates increased to greater than 60% (Russell, Uslan, Rubin, Grogan, & Martin, 2018). However, one retrospective analysis of National Healthcare Safety Network (NHSN) data from a single-center study found that the increasing trend in resistance among *A. baumannii* began to reverse around 2009, and that through 2015, that downward trend has remained relatively consistent through the end of the available data (Russell et al., 2018). These data show a pattern of decreasing resistance across the United States only and do not identify regional variability. A similar trend in resistant isolates was observed in a study of *A. baumannii* in children (aged 1-17) in the United States from 1999-2012, where the overall percentage of isolates resistant to both carbapenems and cephalosporins was higher for both antibiotic classes in 2012 vs. 2009(Russell et al., 2018). However, the peak percentage of resistant isolates was observed in 2008, followed by a steady decrease from that peak up to 2012, where the analysis concluded, in a review of surveillance data acquired through The Surveillance Network (Logan, Gandra, Trett, Weinstein, & Laxminarayan, 2019).

In a review of NHSN surveillance data, trends and treatment options in gram-negative ventilator-associated pneumonia (VAP), as recent as 2018, nearly 50% of U.S. VAP isolates of *A. baumannii* are multi-drug resistant (MDR), with nearly 60% of those isolates being Carbapenem-resistant as reported from two distinct U.S. surveillance efforts (Rhodes, Cruce, O'Donnell, Wunderink, & Hauser, 2018). In another study of hospital-based laboratory results from over 100 hospitals, both

carbapenem-resistant and MDR *A. baumannii complex*, there was a linearly decreasing trend, found to be statistically significant, in the overall rates per 100 hospital admissions from 2013 to 2017 (Gupta et al., 2019). The proportion of isolates in this time frame that were carbapenem non-susceptible and MDR were also decreasing, and these trends were found to be non-significant for carbapenem non-susceptible and significant for MDR, respectively. Again, these results were specific to the United States but did not account for regional variability therein (Gupta et al., 2019).

Studies analyzing resistance to specific antibiotics of last resort have shown varying patterns in resistance. One such antibiotic of last resort is Colistin and, trends in colistin susceptibility among MDR and carbapenem-resistant *A. baumannii* complex have been documented in countries around the world; however, research is lacking in the characterization of such trends within the United States. A study in a university hospital in Sao Paolo, Brazil, found that carbapenem-resistance rates were highest among *A. baumannii* complex isolates and that the percent resistance among these isolates increased from 30% to 70% between 2010 and 2014(Gao, Lyu, & Li, 2017). During this time, approximately 1.4% of *A. baumannii* complex isolates were resistant to Colistin, with slight yearly variation between 2010 and 2014 (Rossi et al., 2017). In a nationwide study of *A. baumannii* complex isolates in China, a consistent and worrying increasing trend in resistance across a wide range of antibiotics and an overall increase in the prevalence of extensively drug resistance (XDR) among *A. baumannii* complex from 11.1% in 2004 to 60.4% in 2014(Gao et al., 2017). In this study, identification of the emergence of Colistin resistance occurred in 2009 with an initial prevalence of 0.9% resistance among *A. baumannii* complex isolates. Resistance to Colistin increased to 30% by 2011 and remained at that level through the end of the study in 2014 (Gao et al., 2017). Colistin resistance occurs among carbapenem-resistant *A. baumannii* complex globally, and that increasing trends in Colistin resistance have been documented. However, within the U.S., there is a lack of data on overall Colistin resistance rates among CRAB in the MuGSI collected data as many Emerging Infection Program (EIP) sites have not tested for Colistin resistance on all collected

CRAB isolates (unpublished CDC data). These data further indicate that regional, national, and global variability can be drastic and that further research is necessary for the United States.

Further evidence of a decreasing trend in the proportion of *A. baumannii* complex displaying resistance is found in studies focusing on specific antibiotics of last resort. Bactrim is another such antibiotic, and a study to assess the rates of resistance to Bactrim found that approximately 50% of isolates tested in North America were resistant overall(Gales et al., 2019). A reduction in resistance was observed over time in these isolates from 1997 to 2016 (Gales et al., 2019). These isolates were collected from various sites in patients hospitalized for a variety of infection types (i.e., bloodstream, pneumonia, and other types of infections)(Gales et al., 2019). Another study found that resistance to Bactrim remained steady for similar years (2003-2012) at between 50% and 60% among isolates from respiratory and bloodstream specimens (Zilberberg, Kollef, & Shorr, 2016). In both cases, the rates of resistance to Bactrim appear similar, but overall trends differ slightly. By assessing these trends again using more recent data might elucidate further trends in these rates. The clinical effectiveness of Bactrim is considered to be low and is usually only recommended when there are few or no other options for treatment(Falagas, Vardakas, & Roussos, 2015; Konca, Tekin, & Geyik, 2021). A review of the evidence was conducted in 2015 to assess the usefulness of Bactrim for the treatment of both MDR and XDR *Acinetobacter spp.* and the resulting conclusions were evidence of very high non-susceptibility among these phenotypes (Falagas et al., 2015). In a recent paper on the susceptibility patterns of MDR *Acinetobacter spp.* among isolates taken from children in a pediatric intensive care unit, it was found that the most effective antimicrobial options were Colistin and Bactrim(Konca et al., 2021). However, in this study, it was also found that more than 50% of these isolates were resistant to Bactrim (Konca et al., 2021).

## CHAPTER II: MANUSCRIPT

# Risk Factors and trends associated with Bactrim non-susceptibility among patients with Carbapenem-resistant *Acinetobacter baumannii* identified through the Emerging Infections Program, 2012 to 2019

Clayton Carmon, Scott Fridkin, and Sandie Bulens

## ABSTRACT

Antibiotic-resistant bacteria have been identified as a serious threat to public health and can lead to high morbidity, mortality, and healthcare costs. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has been a pathogen of concern causing nosocomial infections since the early 1990s. The purpose of this study was to use surveillance data to identify potential risk factors for Bactrim non-susceptibility among CRAB isolates and to identify trends in Bactrim non-susceptibility from 2012-2019. Logistic regression modeling was used to determine the association between independent risk factors and Bactrim non-susceptibility among 1,134 CRAB cases identified through active laboratory-based surveillance between 2012 and 2019. A set of clinical risk factors were identified through literature review and assessed for statistically significant association with Bactrim non-susceptibility. Each risk factor was assessed independently in multivariable models that accounted for potential confounders. Odds ratios and respective 95% confidence intervals were calculated to determine the direction and strength of each risk factor. The final models identified significant associations between several risk factors and Bactrim non-susceptibility: Charleson Score of ≥4 versus ≤1 (OR 0.63, 95% CI 0.45, 0.88), Charleson Score 2 to 3 versus ≤1 (OR 0.70, 95% CI 0.51, 0.95), and pneumonia versus urinary tract infection (UTI) (OR 2.11, 95% CI 1.10, 4.02). The second model used to assess trends in Bactrim non-susceptibility showed that there was a slight increase in the odds of non-susceptibility to Bactrim among patients with CRAB, year over year; however, our model did not show a statistically significant increase during the study period: per one-year increase from 2012-2019 (OR 1.02, 95% CI 0.96, 1.08). Data from this study demonstrated that active surveillance could help elucidate relationships between risk factors and specific antimicrobial resistance among pathogens of concern, as well as potentially identify trends in non-susceptibility over time.

## INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), antibiotic resistance is a serious public health threat("Multi-Site Gram-negative Surveillance Initiative,"). Recent CDC data indicates that an antibiotic-resistant organism infects more than 2.8 million people each year and, of those, over 35,000 die as a result of their infection("Multi-Site Gram-negative Surveillance Initiative,"). Each year, among these cases of infection, are those caused by highly resistant pathogens associated with healthcare settings. One such pathogen is *A. baumannii* complex*,* and treatment options can be limited due to the prevalence of resistance to multiple drug classes and the known relationship between healthcare settings and *A. baumannii* complex (Bulens et al., 2018). *Acinetobacter baumannii* is a pathogen of unique concern due in part to its ability to persist in the environment in addition to the relative ease at which it acquires resistance determinants to antibiotics (Peleg et al., 2008). It does appear that there is a downward trend in the prevalence of resistant *A. baumannii* complex; however, various researchers use a variety of definitions for antibiotic resistance and this lack of a single definition across studies in conjunction with lack of recent data, these recent trends are not fully clear as many studies are becoming out of date. There is a necessity to examine resistance rates in data newer than 2015 in order to determine if these trends are remaining true into the present or if changes in existing patterns are emerging. It seems clear that further investigation into the trends in non-susceptibility to Bactrim among CRAB isolates is essential in determining potential effective treatments for infection by these phenotypes.

The objective of our analysis is twofold, first to assess which existing clinical or healthcare risk factors can be associated with the development of a Bactrim non-susceptible CRAB infection. The

second objective is to document if the percent non-susceptibility to Bactrim has changed in our surveillance population between 2012 and 2019. We analyzed data collected through the CDC's EIP's, Healthcare-Associated Infections Community Interface's (HAIC), Multi-site gram-negative Surveillance Initiative (MuGSI). Cases of carbapenem-resistant *Acinetobacter baumannii* complex (CRAB) were identified by participating EIP program sites that met the established case definition (Bulens et al., 2018). Susceptibility testing was performed at local laboratories using automated antimicrobial susceptibility testing methods (Reno et al., 2014). We hypothesized that non-susceptibility to Bactrim among *A. baumannii* complex infections had decreased steadily between 2012 and 2019 among the full spectrum of patient populations; in addition, we hypothesized that specific patient or healthcare exposures are associated with infections caused by Bactrim non-susceptible CRAB.

## METHODS

### *Surveillance Population, Case Definition, and Identification, Data Collection*

Surveillance data were collected through the Emerging Infections Program's (EIP), Healthcare Associated Infections Community Interface (HAIC), Multi-site Gram-negative Surveillance Initiative (MuGSI). This program collects information on cases of CRAB in 9 states in collaborations with the responsible state health departments and their academic partners in defined catchment areas as described elsewhere (accessed 4/21/2021, MuGSI | HAIC Activities | HAI | CDC). In 2012, Georgia, Minnesota, and Organ were the only participating states. In 2013 the surveillance catchment area was expanded to include Colorado, Maryland, and New Mexico. Tennessee joined the surveillance catchment in 2014, and lastly, in 2018, Connecticut joined (accessed 4/21/2021, MuGSI | HAIC Activities | HAI | CDC). Surveillance case data included in this analysis are from cases with culture dates of January 1, 2012, through December 31, 2019; data is as of January 18, 2021.

A case was defined as the first instance of CRAB per patient in a 30-day period that met the following case definition: “Carbapenem-resistant *Acinetobacter baumannii complex (A. baumannii, A. baumannii complex,* and *A. baumannii calcoaceticus-baumannii complex [*including *A. calcoaceticus])* isolated from normally sterile sites or urine from a resident of the surveillance area ("Multi-Site Gram-negative Surveillance Initiative,")."

Susceptibility testing was generated using automated instruments at the local clinical laboratories (Reno et al., 2014). State partners abstracted generated susceptibility data. Initially, these susceptibility data were categorized into three categories for each drug: susceptible, intermediate, and resistant. These data also included numeric information, depending on the automated testing method, which included Minimum inhibitory concentration (MIC) and zone diameters which are the basis for classification as susceptible, intermediate, or resistant according to Clinical & Laboratory Standards Institute (CLSI) guidelines (Bulens et al., 2018).

State partners actively identified each report of CRAB from all clinical laboratories that serve the residents of the defined catchment area. A standard case report form was collected on each case by reviewing inpatient and outpatient medical records. The following data elements were collected: patient demographics, location of culture collection, risk factors of interest (i.e., healthcare exposures), infections associated with the CRAB culture, underlying comorbid conditions, and the patient's outcome (i.e., died vs. survived) (Bulens et al., 2018). Death was assessed at differing time points, depending on where the patient had the initial culture collected (Healthcare-Associated Infections - Community Interface Data Visualization (HAICViz) | CDC, accessed, 4/21/2021). Hospital inpatients had death assessed at the time of discharge; LTCF or long-term acute care hospital (LTACH) patients had death assessed 30 days after the date of initial culture, and outpatients had death assessed on the date the patient was seen in the outpatient setting (Bulens, et al., 2018). The Charleson Comorbidity Index was calculated based on the underlying conditions collected upon medical record review (McGregor et al.,

2005; McGregor et al., 2006). An LTCF includes patients who stayed in any of the following facility types: nursing home, skilled nursing facility, inpatient hospice, or a physical rehabilitation facility (Bulens et al., 2018).

***Data Cleaning***

To ensure accuracy in the reported drug interpretation and MIC submitted to CDC, we ran data validation reports to identify data entry errors created in SAS 9.4. We assessed if the reported was a valid value according to the CLSI breakpoints for *A. baumannii* (Weinstein, 2020). We had participating EIP sites review the errors and amend them if possible. Reporting of susceptibility for each drug included MIC/Zone diameter and the interpretation of these numeric values as susceptible, intermediate, and resistant. Not all cases included both the MIC/Zone diameter and interpretation. To maximize these data for analysis, we identified those cases where a MIC/Zone diameter was included without an interpretation and used SAS 9.4 to interpret these values based on CLSI breakpoint guidelines (Weinstein, 2020). After this maximization process, only one case was missing interpretation data for Bactrim susceptibility. To create a suitable analysis variable, we then dichotomized the interpretation data as non-susceptible (N.S.) and susceptible (S), where non-susceptible included all interpretations of intermediate or resistant and susceptible included the susceptible interpretations.

***Statistical Analysis***

Variables eligible for inclusion in our analysis were identified through *a priori* literature review. Common variables identified as risk factors for antibiotic resistance include indwelling devices, healthcare exposures, and type of infection (Bassetti et al., 2017; Bedenić et al., 2015; Chen et al., 2018; "Multi-Site Gram-negative Surveillance Initiative,"; Wieland et al., 2018). Based on *a priori* knowledge, we searched the surveillance data set for variables that fit into the categories for inclusion in the analysis as potential risk factors for Bactrim non-susceptibility (Table 3). Confounders were similarly

identified through *a priori* knowledge, and these potential confounders were included in the final multivariable model to obtain adjusted Odds Ratios for the association between our identified risk factors and Bactrim non-susceptibility (Table 2). All measures of association were tested for significance at the 0.05 alpha level.

***Logistic Regression Modeling: assessment of risk factors and for time trend analysis***

The goal of our analysis was twofold. First to use modeling to assess whether risk factors, as identified from our a priori search of the literature, are associated with a patient having an infection with CRAB that is also non-susceptible to Bactrim. These risk factors could be used for prevention efforts. The second goal was to use logistic regression to assess if the odds of CRAB non-susceptible to Bactrim are changing over time in our surveillance population.

Logistic regression modeling was used in SAS 9.4 to assess both risk factors associated with Bactrim non-susceptibility and the relationship of non-susceptibility with different years of surveillance data. Crude odds ratios (Table 3) were obtained for the relationships between the individual risk factors and the outcome of interest in this analysis: Non-susceptibility to Bactrim. The final multivariable models included each risk factor of interest, and the *a priori* identified confounders of age, sex, State, residence in the four days prior to culture collection, ICU stay in the seven days prior to culture collection, and patient race. We used these separate multivariable models to obtain the adjusted Odds Ratios for each of the risk factors of interest.

Logistic regression modeling was used to assess the time trends of Bactrim non-susceptibility from 2012 to 2019 (Table 4). We created a continuous variable for year and built a crude model to assess the odds of Bactrim non-susceptibility for each one-year increase. We then built a multivariable model using the previously identified confounders (age, sex, race, residence, and recent ICU stay) and obtained the adjusted odds ratio for Bactrim non-susceptibility for each year increase in the data.

Exploratory analysis was conducted on potential outcomes using simple 2x2 tables where we assessed the relationship of potential outcomes for case-patients with infection by Bactrim non-susceptible CRAB (Table 1b). These outcomes include hospitalization in the 30 days following culture collection, ICU admission in the seven days after culture collection, and death. The relative risk of these outcomes was calculated using Cochran-Mantel-Haenszel methods in SAS 9.4 to obtain the estimated measure of association and its corresponding 95% confidence interval.

## RESULTS

Overall, 1134 CRAB cases met the case definition between 2012 and 2019. Out of these cases of CRAB, 448 were identified as being non-susceptible to Bactrim (Table 1a). Patients were more likely to be of black race, between the ages of 50-64 years, and to be from the state of M.D. or G.A. (Table 1a). Initial cultures were most likely collected in the Emergency Room (E.R.), which is consistent with the finding that most patients were in either an LTCF or private residence in the four days prior to the date of culture (Table 1a.). A wide range of underlying conditions were identified through case identification, with several case-patients having more than one underlying condition identified (Table 1a). The frequency of identified underlying co-morbidities, as found on medical record review, was diverse. On average, cases had 3.5 underlying conditions identified with a range of 0-10.

A simple exploratory analysis of potential outcomes of Bactrim non-susceptible CRAB infections among cases showed that cases of CRAB that were non-susceptible to Bactrim more likely to be hospitalized in the 30 days following culture collection unadjusted RR 1.21 (95% CI 1.14, 1.29) than were cases that had Bactrim susceptible CRAB. Similarly, cases with Bactrim non-susceptible CRAB were more likely to be admitted to the ICU within seven days of culture collection unadjusted RR 1.34 (95% CI 1.11, 1.62) than were cases that had Bactrim susceptible CRAB (Table 1b).

Our assessment of potential confounders for our model to assess the significance of risk factors for the development of Bactrim non-susceptible CRAB is presented in Table 2. Although not significant, we choose to control for age, sex, and race, considering we know that these factors can vary significantly in the underlying populations that make up the EIP catchment area. We also included year in the model, although it was not significant, as a way to control the change in the catchment population over time. Additionally, we decided to control for where the patient resided four days prior to culture collection due to the potential relationships that exist between this potential confounder and both Bactrim non-susceptibility and having CRAB. A stay in the ICU was found to be both a possible confounder and risk factor for our outcome of interest and was included in the model.

Of the potential risk factors included in the analysis, only CVC and Urinary Catheter were significantly associated with Bactrim non-susceptibility on crude analysis (Table 3). The odds of having Bactrim non-susceptible CRAB among those with a CVC was 1.39 (95% CI 1.08, 1.78) times the odds of having Bactrim non-susceptibility among those without a CVC. The odds of having Bactrim non-susceptible CRAB among those with a urinary catheter was 1.34 (95% CI 1.04, 1.71) times the odds of having Bactrim non-susceptible CRAB among those without a urinary catheter. After adjusting for age, sex, race, state, ICU stay in the prior seven days, and the location that the case was residing four days prior to culture collection, these findings were no longer significant, 1.18 (95% CI 0.89, 1.56) for CVC and 1.06 (95% CI 0.81, 1.53). After adjusting for these potential confounders based on *a priori* literature review (Table 2), two risk factors became significantly associated with Bactrim non-susceptibility among CRAB cases meeting the established case definition (Table 3). These factors were infection type and Charleson Score (severity of illness score). Within the categorical variable of infection type, pneumonia became the only infection type significantly associated with Bactrim non-susceptibility versus urinary tract infection (UTI). In fact, the odds of Bactrim non-susceptibility among those with pneumonia was 2.11 (95% CI 1.10, 4.02) times the odds of Bactrim non-susceptibility among those with a UTI. Regarding

the Charleson score, higher scores appear to be protective against Bactrim non-susceptible CRAB in these surveillance data with the odds of Bactrim non-susceptible CRAB among those with Charleson score of 2 to 3 versus less than or equal to 1 being 0.70 (95% CI 0.51, 0.95) and the odds of Bactrim non-susceptible CRAB among those with a Charleson score greater than or equal to 4 versus less than or equal to 1 being 0.63 (95% CI 0.45, 0.88). Interestingly, none of the healthcare exposures in the year prior to culture collection were significantly associated with Bactrim non-susceptibility among CRAB cases in both the unadjusted and adjusted models.

The percent non-susceptible to Bactrim among the CRAB cases was 49% in 2012, 40%% in 2013, 32%% in 2014, 42%% in 2015, 45%% in 2016, 34%% in 2017, 38%% in 2018, and 38%% in 2019 (Table 5). Because we saw a downward trend in percent non-susceptible over time, we conducted a test for trend, using a simple logistic regression model (Table 4). The crude analysis showed that there might be a small decrease in the proportion of Bactrim non-susceptible cases per year from 2012 to 2019; however, this association was not significant OR 0.97 (0.92, 1.02). Upon adjusting for state, age, race, and ICU in the prior seven days, the relationship remains null, with an odds of Bactrim non-susceptibility among CRAB cases being 1.02 (95% CI 0.96, 1.08) per one-year increase in these data. This suggests that while absolute numbers and proportions of CRAB cases that are Bactrim non-susceptible might be decreasing from 2012 to 2019, there does not appear to be any significant association between year and Bactrim non-susceptibility.

## DISCUSSION

Among the 1135 cases of CRAB identified through the EIP, 448 were determined to be non-susceptible to Bactrim by the local clinical laboratories during our study period. Patients who were male (at the time of birth), were between the ages of 50-64 years of age, and of black race were the most frequent to have Bactrim non-susceptible CRAB. Cases with a diagnosis of pneumonia, controlling for

age, race, sex, and state, were significantly more likely to be Bactrim non-susceptible. However, the observed percent non-susceptibly to Bactrim among the CRAB cases appeared to decrease over time; this decline was not significant after accounting for confounders.

***Surveillance for CRAB***

It has become clear, since the 1990s, that understanding the epidemiology and clinical manifestations of *A. baumannii* complex is an important goal in finding effective prevention and treatment options(Kaye & Pogue, 2015; Peleg et al., 2008; Wieland et al., 2018). Infections caused by CRAB are often challenging to treat and result in poor outcomes and increased healthcare burdens both in and outside of the United States(Kurihara, Sales, Silva, Maciel, & Simionatto, 2020). Surveillance initiatives, such as MuGSI, allow for the detection and identification of epidemiological, genetic, and time trends for CRAB and provide insight into potential methods for addressing and reducing the burden of disease caused by CRAB and other concerning pathogens ("Multi-Site Gram-negative Surveillance Initiative,"). These surveillance activities can also provide insight into potential risk factors in the development of both disease caused by CRAB and risk factors that might be related to the development of further resistance to other antimicrobial agents (Ramirez, Bonomo, & Tolmasky, 2020).

***Infection Outcomes***

The simple analysis conducted here on the potential outcomes gathered through these surveillance efforts points to worse outcomes in cases where there is resistance to one or more antimicrobial where the risk of being hospitalized within 30 days of culture collection among cases with Bactrim non-susceptible CRAB was 1.21 (95% CI 1.14, 1.29) times that of cases with Bactrim susceptible CRAB. Similarly, the risk of ICU admission within seven days of culture collection among cases with Bactrim susceptible CRAB was 1.34 (95% CI 1.11, 1.62) times that of case cases with Bactrim susceptible CRAB. Recent studies show that infections caused by CRAB that have additional resistance to one or

more antimicrobials tend to result in higher mortality and morbidity (Dickstein et al., 2019). We found that the crude risk of both hospitalization and ICU admission was higher among CRAB cases that were additionally non-susceptible to Bactrim, 1.21 (95% CI 1.14, 1.29) and 1.34 (95% CI 1.11, 1.62) respectively, which supports existing knowledge that antimicrobial resistance contributes to increased healthcare utilization and costs (Friedman, Temkin, & Carmeli, 2016).

***Risk Factors for Bactrim Non-Susceptibility***

Established and known risk factors for the development of CRAB and other antimicrobial-resistant infections point to healthcare exposures, stays in LTCFs, certain underlying conditions, age, higher Charleson Scores, and the use of certain indwelling devices (Bassetti et al., 2017; Bedenić et al., 2015; Chen et al., 2018; Wieland et al., 2018). We set out to identify specific independent risk factors for developing an infection by Bactrim non-susceptible CRAB utilizing the MuGSI surveillance dataset. We found, upon analysis, that these known risk factors for CRAB infection do not necessarily stay true for identifying risk factors for Bactrim non-susceptible CRAB infection in our dataset. While indwelling devices are known to be a risk factor for acquiring CRAB, there was not a significant association between any of our indwelling device risk factors and Bactrim non-susceptibility. This seems to point to potential unidentified relationships between indwelling device use and other factors.

In previous studies, Charleson Scores have been considered risk factors for developing antimicrobial-resistant *A. baumannii* infections (Bassetti et al., 2017). We identified a counter-intuitive association between Charleson score and Bactrim non-susceptibility that seems to point to higher Charleson Scores being somewhat protective against the development of Bactrim non-susceptibility among CRAB cases after controlling for age, sex, state, race, ICU stay in the prior seven days, and residence in the four days prior to culture collection. This finding raises questions about the underlying causes of this relationship and points to the need for more detailed study and potentially using more

complex models to assess the potential secondary relationships or effect measure modification with additional factors. Since Charleson Scores are a composite representation of patient-level co-morbidities, analyzing the individual co-morbidities and their relationship with Bactrim susceptibility may be warranted as these co-morbidities may play a crucial role in the potential for additional exposures related to Bactrim non-susceptibility such as previous Bactrim use and additional healthcare exposures not captured in this dataset (McGregor et al., 2005; McGregor et al., 2006).

Type of infection is another risk factor we analyzed and found that, when compared to UTI, pneumonia had a stronger relationship with Bactrim non-susceptible CRAB with an odds ratio of 2.11 (95% CI 1.10, 4.02). This finding may point to several underlying relationships of importance regarding Bactrim non-susceptibility among CRAB cases. Since CRAB is known for causing nosocomial infections, especially pneumonia associated with ventilator use, there may be some secondary relationships between the location of acquisition of CRAB and the development of pneumonia which in turn may play a part in additional exposures such as antibiotic therapy and co-morbidities (Djordjevic et al., 2016). More complex models that include the potential for effect measure modification might be helpful in better understanding pneumonia as a risk factor for Bactrim non-susceptible CRAB. However, our findings point to the importance of pneumonia in potential efforts to reduce the development of Bactrim non-susceptible CRAB in healthcare settings.

Upon analyzing the time trends in Bactrim non-susceptibility in our dataset, we found that the relationship between year and Bactrim non-susceptibility remained steady from 2012 to 2019, where the odds of Bactrim non-susceptibility did not change per one year increase in our data. From 2012 to 2019, the overall percent of isolates that were non-susceptible to Bactrim remained between 30% and 50% per year (Table 5). This supports previous literature pointing to a steady trend in Bactrim non-susceptibility, remaining about 50% in several studies over time, among CRAB isolates (Falagas et al., 2015; Gales et al., 2019; Konca et al., 2021; Zilberberg et al., 2016). While a decreasing trend would be

beneficial for the future potential of Bactrim as a treatment for CRAB infection, the fact that the proportion of Bactrim resistant isolates is remaining steady is encouraging in that there does not appear to be growing resistance based on these surveillance data.

There were limitations in this study. First, these surveillance data overwhelmingly come from just two states out of the nine total participants in the surveillance program. This limits the generalizability of identified risk factors from these data and makes determining the importance of these risk factors are on a larger scale difficult. Second, these surveillance activities do not collect information on previous antibiotic use, which is potentially a significant risk factor for developing resistance to antibiotics. Third, due to the nature of these surveillance data, it is impossible to make conclusions on the potential causal relationships between these risk factors and Bactrim non-susceptibility among CRAB isolates. Fourth, with so few cases of CRAB each year in these surveillance data, our analysis may not have been sufficiently powered to identify significant associations between our risk factors and Bactrim non-susceptibility and trends in non-susceptibility over time. Fifth, we conducted only simple analyses using single exposure models that did not account for the potential of effect measure modification or statistical interaction between risk factors or confounders. Lastly, there may be unobserved and uncaptured risk factors and confounders that play a crucial role in the relationship between identified risk factors and Bactrim non-susceptibility.

Despite these limitations, this study has some strengths. Utilizing surveillance data such as these can be an essential and powerful tool in gaining initial insight into potential risk factors to look out for in clinical settings that might help mitigate the development of Bactrim non-susceptibility in CRAB cases. Further, these initial results may be significant in developing more complex and stringent studies to identify further the relationships between these risk factors and Bactrim non-susceptibility.

In summary, this study has demonstrated that there are identifiable risk factors associated with Bactrim non-susceptibility among CRAB cases. Identifying these risk factors might contribute to a better understanding of how to recognize which cases might be Bactrim non-susceptible and mitigate the development of Bactrim non-susceptibility among CRAB cases. This study also supports continued active surveillance for identifying both trends in non-susceptibility to antimicrobials and the understanding of relationships between risk factors for and outcomes of antimicrobial resistance.

Bibliography

Bassetti, M., Carnelutti, A., & Peghin, M. (2017). Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. *Expert Rev Anti Infect Ther, 15*(1), 55-65. doi:10.1080/14787210.2017.1251840

Bedenić, B., Beader, N., Godič-Torkar, K., Vranić-Ladavac, M., Luxner, J., Veir, Z., . . . Zarfel, G. (2015). Nursing Home as a Reservoir of Carbapenem-Resistant Acinetobacter baumannii. *Microbial Drug Resistance, 21*(3), 270-278. doi:10.1089/mdr.2014.0157

Bulens, S. N., Yi, S. H., Walters, M. S., Jacob, J. T., Bower, C., Reno, J., . . . Kallen, A. J. (2018). Carbapenem-Nonsusceptible Acinetobacter baumannii, 8 U.S. Metropolitan Areas, 2012-2015. *Emerging infectious diseases, 24*(4), 727-734. doi:10.3201/eid2404.171461

Chen, C. H., Kuo, H. Y., Hsu, P. J., Chang, C. M., Chen, J. Y., Lu, H. H., . . . Liou, M. L. (2018). Clonal spread of carbapenem-resistant Acinetobacter baumannii across a community hospital and its affiliated long-term care facilities: A cross sectional study. *J Microbiol Immunol Infect, 51*(3), 377-384. doi:10.1016/j.jmii.2017.08.001

Dickstein, Y., Lellouche, J., Ben Dalak Amar, M., Schwartz, D., Nutman, A., Daitch, V., . . . Group, A. S. (2019). Treatment Outcomes of Colistin- and Carbapenem-resistant Acinetobacter baumannii Infections: An Exploratory Subgroup Analysis of a Randomized Clinical Trial. *Clin Infect Dis, 69*(5), 769-776. doi:10.1093/cid/ciy988

Djordjevic, Z. M., Folic, M. M., Folic, N. D., Gajovic, N., Gajovic, O., & Jankovic, S. M. (2016). Risk factors for hospital infections caused by carbapanem-resistant Acinetobacter baumannii. *J Infect Dev Ctries, 10*(10), 1073-1080. doi:10.3855/jidc.8231

Falagas, M. E., Vardakas, K. Z., & Roussos, N. S. (2015). Trimethoprim/sulfamethoxazole for Acinetobacter spp.: A review of current microbiological and clinical evidence. *Int J Antimicrob Agents, 46*(3), 231-241. doi:10.1016/j.ijantimicag.2015.04.002

Friedman, N. D., Temkin, E., & Carmeli, Y. (2016). The negative impact of antibiotic resistance. *Clin Microbiol Infect, 22*(5), 416-422. doi:10.1016/j.cmi.2015.12.002

Gales, A. C., Seifert, H., Gur, D., Castanheira, M., Jones, R. N., & Sader, H. S. (2019). Antimicrobial Susceptibility of Acinetobacter calcoaceticus-Acinetobacter baumannii Complex and Stenotrophomonas maltophilia Clinical Isolates: Results From the SENTRY Antimicrobial Surveillance Program (1997-2016). *Open Forum Infect Dis, 6*(Suppl 1), S34-s46. doi:10.1093/ofid/ofy293

Gao, L., Lyu, Y., & Li, Y. (2017). Trends in Drug Resistance of Acinetobacter baumannii over a 10-year Period: Nationwide Data from the China Surveillance of Antimicrobial Resistance Program. *Chin Med J (Engl), 130*(6), 659-664. doi:10.4103/0366-6999.201601

Gupta, V., Ye, G., Olesky, M., Lawrence, K., Murray, J., & Yu, K. (2019). Trends in resistant Enterobacteriaceae and Acinetobacter species in hospitalized patients in the United States: 2013-2017. *BMC Infectious Diseases, 19*(1), 742. doi:10.1186/s12879-019-4387-3

Kaye, K. S., & Pogue, J. M. (2015). Infections Caused by Resistant Gram-Negative Bacteria: Epidemiology and Management. *Pharmacotherapy, 35*(10), 949-962. doi:10.1002/phar.1636

Konca, C., Tekin, M., & Geyik, M. (2021). Susceptibility Patterns of Multidrug-Resistant Acinetobacter baumannii. *Indian J Pediatr, 88*(2), 120-126. doi:10.1007/s12098-020-03346-4

Kurihara, M. N. L., Sales, R. O., Silva, K. E. D., Maciel, W. G., & Simionatto, S. (2020). Multidrug-resistant Acinetobacter baumannii outbreaks: a global problem in healthcare settings. *Rev Soc Bras Med Trop, 53*, e20200248. doi:10.1590/0037-8682-0248-2020

Logan, L. K., Gandra, S., Trett, A., Weinstein, R. A., & Laxminarayan, R. (2019). Acinetobacter baumannii Resistance Trends in Children in the United States, 1999-2012. *J Pediatric Infect Dis Soc, 8*(2), 136-142. doi:10.1093/jpids/piy018

McGregor, J. C., Kim, P. W., Perencevich, E. N., Bradham, D. D., Furuno, J. P., Kaye, K. S., . . . Harris, A. D. (2005). Utility of the Chronic Disease Score and Charlson Comorbidity Index as co-morbidity measures for use in epidemiologic studies of antibiotic-resistant organisms. *Am J Epidemiol, 161*(5), 483-493. doi:10.1093/aje/kwi068

McGregor, J. C., Perencevich, E. N., Furuno, J. P., Langenberg, P., Flannery, K., Zhu, J., . . . Harris, A. D. (2006). Co-morbidity risk-adjustment measures were developed and validated for studies of antibiotic-resistant infections. *J Clin Epidemiol, 59*(12), 1266-1273. doi:10.1016/j.jclinepi.2006.01.016

Multi-Site Gram-negative Surveillance Initiative. (March 16, 2021). Retrieved from https://www.cdc.gov/hai/eip/mugsi.html

Peleg, A. Y., Seifert, H., & Paterson, D. L. (2008). Acinetobacter baumannii: emergence of a successful pathogen. *Clin Microbiol Rev, 21*(3), 538-582. doi:10.1128/CMR.00058-07

Ramirez, M. S., Bonomo, R. A., & Tolmasky, M. E. (2020). Carbapenemases: Transforming Acinetobacter baumannii into a Yet More Dangerous Menace. *Biomolecules, 10*(5). doi:10.3390/biom10050720

Reno, J., Schenck, C., Scott, J., Clark, L. A., Wang, Y. F., Ray, S., . . . Jacob, J. T. (2014). Querying automated antibiotic susceptibility testing instruments: a novel population-based active surveillance method for multidrug-resistant gram-negative bacilli. *Infection control and hospital epidemiology, 35*(4), 336-341. doi:10.1086/675608

Rhodes, N. J., Cruce, C. E., O'Donnell, J. N., Wunderink, R. G., & Hauser, A. R. (2018). Resistance trends and treatment options in Gram-negative ventilator-associated pneumonia. *Current Infectious Disease Reports, 20*(2). doi:10.1007/s11908-018-0609-x.

Rossi, F., Girardello, R., Cury, A. P., Di Gioia, T. S., Almeida, J. N., Jr., & Duarte, A. J. (2017). emergence of colistin resistance in the largest university hospital complex of Sao Paulo, Brazil, over five years. *Braz J Infect Dis, 21*(1), 98-101. doi:10.1016/j.bjid.2016.09.011

Russell, D. L., Uslan, D. Z., Rubin, Z. A., Grogan, T. R., & Martin, E. M. (2018). Multidrug Resistant Acinetobacter baumanii: A 15-Year Trend Analysis. *Infection control and hospital epidemiology, 39*(5), 608-611. doi:10.1017/ice.2018.52

Weinstein, M. P., Lewis, J. S., Bobenchik, A. M., Campeau, S., Cullen, S. K., Galas, M. F., Gold, H., Humphries, R. M., Kirn, T. J., Limbago, B., Mathers, A. J., Mazzulli, T., Satlin, M., Shuetz, A. N., Simner, P. J., Tamma, P. D. (2020). CLSI M100-ED30:2020 Performance Standards for Antimicrobial Susceptibility Testing, 30th Edition. Retrieved from http://em100.edaptivedocs.net/GetDoc.aspx?doc=CLSI M100 ED30:2020&xormat=SPDF&src=BB

Wieland, K., Chhatwal, P., & Vonberg, R.-P. (2018). Nosocomial outbreaks caused by Acinetobacter baumannii and Pseudomonas aeruginosa: Results of a systematic review. *American Journal of Infection Control, 46*(6), 643-648. doi:https://doi.org/10.1016/j.ajic.2017.12.014

Wong, D., Nielsen, T. B., Bonomo, R. A., Pantapalangkoor, P., Luna, B., & Spellberg, B. (2017). Clinical and Pathophysiological Overview of Acinetobacter Infections: a Century of Challenges. *Clinical Microbiology Reviews, 30*(1), 409-447. doi:10.1128/CMR.00058-16

Zilberberg, M. D., Kollef, M. H., & Shorr, A. F. (2016). Secular trends in Acinetobacter baumannii resistance in respiratory and blood stream specimens in the United States, 2003 to 2012: A survey study. *J Hosp Med, 11*(1), 21-26. doi:10.1002/jhm.2477

**Table 1a: Demographics and Underlying Conditions of case patients identified through Multi-Site Gram Negative Surveillance Initiative overall and by Carbapenem-resistant *Acinetobacter baumannii* isolate susceptibility to Bactrim**

| | **OVERALL N = 1134 COUNT (%)** | Non-Susceptible* n = 448 **COUNT (%)** | Susceptible* n = 685 **COUNT (%)** |
|---|---|---|---|
| **Gender** | | | |
| **Male** | 763 (67.3%) | 309 (69%) | 454 (66.3%) |
| **Female** | 371 (32.7%) | 139 (31%) | 231 (33.7%) |
| **Age** | | | |
| **0-18** | 6 (0.53%) | 2 (0.45%) | 4 (0.58%) |
| **19-49** | 310 (27.3% | 128 (28.8%) | 181 (26.4%) |
| **50-64** | 344 (30.3%) | 134 (29.9%) | 210 (30.66%) |
| **65-79** | 327 (28.8%) | 122 (27.2%) | 205 (29.9%) |
| **80+** | 147 (13%) | 61 (13.6 %) | 85 (12.4 %) |
| **Race** | | | |
| **White[1]** | 417 (36.8%%) | 170 (37.9%) | 246 (35.9%) |
| **Black** | 634 (55.9%) | 263 (58.7%) | 371 (54.2%) |
| **American Indian** | 4 (0.35%) | 1 (0.22%) | 3 (0.44%) |
| **Asian** | 20 (1.76%) | 6 (1.34%) | 14 (2.04%) |
| **Pacific Islander** | None | None | None |
| **Unknown** | 59 (5.20 %) | 8 (1.8%) | 51 (7.45%) |
| **State** | | | |
| **Colorado** | 35 (3.09%) | 16 (3.6%) | 19 (2.8%) |
| **Connecticut** | 25 (2.2%) | 6 (1.3%) | 19 (2.8%) |
| **Georgia** | 473 (41.7%) | 222 (49.6%) | 250 (36.5%) |
| **Maryland** | 457 (40.3%) | 160 (35.7%) | 297 (43.4%) |
| **Minnesota** | 41 (3.6%) | 11 (2.5%) | 30 (4.4%) |
| **New Mexico** | 9 (0.79%) | 5 (1.1%) | 4 (0.58%) |
| **New York** | 11 (0.97%) | 0 (0%) | 11 (1.6%) |
| **Oregon** | 9 (0.79%) | 1 (0.22%) | 8 (1.2%) |
| **Tennessee** | 74 (6.53%) | 27 (6%) | 47 (6.9%) |
| **Residence[2]** | | | |
| **Private Residence** | 321 (28.3%) | 127 (28.4%) | 194 (28.3%) |
| **Hospital Inpatient** | 271 (23.9%) | 129 (28.8%) | 142 (20.7%) |
| **LTACH[3]** | 53 (4.7%) | 15 (3.4%) | 38 (5.6%) |
| **LTCF[4]** | 474 (41.8%) | 177 (38.5%) | 296 (43.2%) |
| **Other** | 1 (0.09%) | 0 | 1 (0.15%) |
| **Unknown** | 14 (1.23%) | 0 | 14 (2.04%) |
| **Location of Collection** | | | |
| **ER[6]** | 414 (36.5%) | 193 (43.1%) | 221 (32.3%) |

| | | | |
|---|---|---|---|
| **ICU[7]** | 143 (12.6%) | 76 (17.0%) | 67 (9.8%) |
| **LTACH[3]** | 42 (3.7%) | 12 (2.7%) | 30 (4.4%) |
| **LTCF[4]** | 207 (18.3%) | 33 (7.4%) | 173 (25.3%) |
| **OPCL[8]** | 36 (3.2%) | 10 (2.2%) | 26 (3.8%) |
| **OTHIP[9]** | 238 (21%) | 117 (26.1%) | 121 (17.7%) |
| **Underlying Conditions[**]** | | | |
| **Chronic Liver Disease** | 63 (5.6%) | 20 (4.5%) | 43 (6.3%) |
| **Chronic Pulmonary Disease** | 292 (25.8%) | 119 (26.6%) | 173 (26.3%) |
| **Chronic renal insufficiency** | 214 (18.9%) | 85 (19%) | 129 (18.8%) |
| **Chronic skin breakdown** | 104 (9.2%) | 41 (9.2%) | 63 (9.2%) |
| **Congestive heart failure** | 202 (17.8%) | 87 (19.4%) | 115 (16.8%) |
| **Current Smoker** | 153 (13.5%) | 60 (13.4%) | 93 (13.6%) |
| **Stroke** | 214 (18.9%) | 102 (22.8%) | 112 (16.4%) |
| **Decubitus** | 602 (53.1%) | 237 (52.9%) | 364 (53.1%) |
| **Dementia/Chronic cognitive deficit** | 169 (14.9%) | 66 (14.7%) | 102 (14.9%) |
| **Diabetes** | 442 (39%) | 176 (39.3%) | 265 (38.7%) |
| **Hemiplegia/paraplegia** | 243 (21.4%) | 85 (19%) | 158 (23.1%) |
| **Myocardial Infarction** | 72 (6.4%) | 29 (6.5%) | 43 (6.3%) |
| **Neurological Problems** | 337 (29.7%) | 138 (30.8%) | 199 (29.1%) |
| **Obesity** | 106 (9.4%) | 36 (8%) | 69 (10.1%) |
| **Peripheral Vascular Disease** | 108 (9.5%) | 35 (7.8%) | 73 (10.7%) |
| **Solid Tumor (non-metastatic)** | 63 (5.6%) | 29 (6.5%) | 33 (4.8%) |
| **Urinary tract problems/Abnormalities** | 345 (30.4%) | 133 (29.7%) | 212 (31%) |

*One case patient is missing data on Bactrim susceptibility

**Some case patients have more than one underlying condition [1] One case patient missing data on Bactrim susceptibility among those that are of the white race

[3]Where the patient resided 4 days prior to culture collection

[4]Long-term Acute Care Hospital

[5]Long-term Care Facility

[6]Emergency Room

[7]Intensive Care Unit

[8]Outpatient Clinic/Doctors Office

[9]Other Hospital Inpatient Unit

| Table 1b: Characteristics of infection outcome among case patients and the relative risk of outcome among case patients with carbapenem-resistant *Acinetobacter baumannii* isolates the are non-susceptible to Bactrim | | | |
|---|---|---|---|
| | **Non-Susceptible Count (%)** | **Susceptible Count (%)** | **R.R. (95%CI)** |
| **HOSPITALIZED[3]** | | | |
| **YES** | 381 (85%) | 450 (70.3%) | 1.21 (1.14,1.29) |
| **NO** | 67 (15%) | 190 (29.7%) | - |
| **ICU After[4]** | | | |
| **YES** | 149 (33.4%) | 158 (24.8%) | 1.34 (1.11, 1.62) |
| **NO** | 297 (66.6% | 478 (75.2%) | - |
| **Outcome[5]** | | | |
| **DIED** | 83 (18.6%) | 98 (15.3%) | 1.21 (0.92, 1.58) |
| **SURVIVED** | 364 (81.4%) | 541 (84.7%) | - |
| | | | |

[10]Hospitalized within 30-days of culture collection, 46 missing

[11]Admitted to ICU on the day of culture or within 7 days of culture collection, 52 missing

[12]48 missing

| Table 2: Patient, temporal, and geographic characteristics of cases patients potentially associated with Bactrim non-susceptibility or other potential predictors of non-susceptibility | | | |
|---|---|---|---|
| | **Non-Susceptible Count (%)** | **Susceptible Count (%)** | **OR (95% CI)** |
| **Age** | | | |
| **0-49** | 131 (29.4%) | 185 (27.0%) | *Ref* |
| **50-64** | 134 (29.9%) | 210 (30.7%) | 0.90 (0.66, 1.23) |
| **65-79** | 122 (27.2%) | 205 (29.9%) | 0.84 (0.61, 1.15) |
| **80+** | 61 (13.6 %) | 85 (12.4 %) | 1.01 (0.68, 1.51) |
| **Sex** | | | |
| **Male** | 309 (69%) | 454 (66.3%) | 1.13 (0.88, 1.46) |
| **Female** | 139 (31%) | 231 (33.7%) | *ref* |
| **State** | | | |
| **All other States** | 66 (14.7%) | 138 (20.1%) | *ref* |
| **Georgia** | 222 (49.6%) | 250 (36.5%) | 1.86 (1.32, 2.62) |
| **Maryland** | 160 (35.7%) | 297 (43.4%) | 1.13 (0.79, 1.60) |
| **Race** | | | |
| **Non-Black** | 177 (40.2%) | 262 (41.3%) | *ref* |
| **Black** | 263 (59.8%) | 372 (58.7%) | 1.05 (0.82, 1.34) |
| **Year** | | | |
| **2012** | 56 (12.5%) | 58 (8.5%) | *Ref* |
| **2013** | 75 (16.7%) | 113 (16.5%) | 0.69 (0.43, 1.1) |
| **2014** | 51 (11.4%) | 109 (15.9%) | 0.49 (0.30, 0.79) |
| **2015** | 72 (16.1%) | 98 (14.3%) | 0.76 (0.47, 1.23) |
| **2016** | 53 (11.8%) | 64 (9.3%) | 0.86 (0.51, 1.44) |
| **2017** | 42 (9.4%) | 82 (12.0%) | 0.53 (0.32, 0.90) |
| **2018** | 46 (10.3%) | 75 (11.0%) | 0.64 (0.38, 1.07) |
| **2019** | 53 (11.8%) | 86 (12.6%) | 0.64 (0.29, 1.05) |
| **ICU Prior 7 days** | | | |
| **Yes** | 71 (15.8%) | 77 (11.5%) | 1.45 (1.02, 2.05) |
| **No/Unknown** | 377 (84.2%) | 592 (88.5%) | *ref* |
| **Residence** | | | |
| **LTCF*** | 176 (39.5%) | 296 (45.6%) | 0.85 (0.63, 1.14) |
| **Inpatient/LTACH**** | 149 (33.4%) | 180 (27.7%) | 1.18 (0.86, 1.63) |
| **Private Residence** | 121 (27.1%) | 173 (26.7%) | *ref* |

*Long-term Care Facility

**Long Term Acute Care Hospit

**Table 3: Crude and adjusted Odds Ratio estimates of clinical factors potentially associated with Bactrim non-susceptibility among carbapenem-resistant *Acinetobacter baumannii* case isolates from 2012-2019**

| | Non-Susceptible N = 448 Count (%) | Susceptible N = 685 Count (%) | cOR (95% CI) | aOR (95% CI)* |
|---|---|---|---|---|
| **Clinical Characteristics** | | | | |
| **Central Vascular Catheter** | | | | |
| **Yes** | 174 (38.4%) | 215 (31.4%) | 1.39 (1.08, 1.78) | 1.18 (0.89, 1.56) |
| **No** | 274 (61.2%) | 470 (68.6%) | *Ref* | *ref* |
| **Urinary Catheter** | | | | |
| **Yes** | 297 (66.3%) | 408 (59.6%) | 1.34 (1.04, 1.71) | 1.06 (0.81, 1.39) |
| **No** | 151 (33.7%) | 277 (40.4%) | *Ref* | *ref* |
| **Gastrostomy Tube** | | | | |
| **Yes** | 123 (27.5%) | 159 (23.2%) | 1.25 (0.95, 1.64) | 1.14 (0.85, 1.53) |
| **No** | 325 (72.5%) | 526 (76.8%) | *Ref* | *ref* |
| **Tracheostomy** | | | | |
| **Yes** | 96 (21.4%) | 131 (19.1%) | 1.15 (0.86, 1.55) | 1.06 (0.77, 1.45) |
| **No** | 352 (78.6%) | 554 (80.9%) | *Ref* | *ref* |
| **Charleson Score Median (IQR)** | 2.0 (1, 4) | 2.0 (1, 4) | | |
| **≥ 4** | 130 (29.0%) | 209 (32.1%) | 0.76 (0.56, 1.04) | 0.63 (0.45, 0.88) |
| **2 – 3** | 176 (39.3%) | 268 (41.2%) | 0.80 (0.60, 1.08) | 0.70 (0.51, 0.95) |
| **≤ 1** | 142 (31.7%) | 174 (26.7%) | *ref* | *ref* |
| **Specimen Collection Type** | | | | |
| **Blood or Normally Sterile Site** | 135 (30.5%) | 177 (26.5%) | 1.22 (0.93, 1.59) | 1.15 (0.86, 1.54) |
| **Urine** | 308 (69.5%) | 491 (73.5%) | *ref* | *ref* |
| **Infection Type** | | | | |
| **Urinary Tract Infection** | 211 (55.5%) | 316 (60.3%) | *ref* | *ref* |
| **Blood Stream Infection** | 110 (28.9%) | 137 (26.2%) | 1.20 (0.89, 1.63) | 1.26 (0.89, 1.78) |
| **Pneumonia** | 25 (6.6%) | 21 (4.0%) | 1.78 (0.97, 3.27) | 2.11 (1.10, 4.02) |
| **Other** | 34 (8.9%) | 50 (9.5%) | 1.02 (0.64, 1.63) | 1.00 (0.61, 1.64) |
| **Septic shock** | | | | |
| **Yes** | 38 (8.5%) | 56 (8.2%) | 1.04 (0.68, 1.60) | 1.12 (0.70, 1.77) |
| **No/Unknown** | 410 (91.5%) | 629 (91.8%) | *ref* | *ref* |
| **Exposure to Healthcare Settings** | | | | |
| **Hospitalized in Prior year** | | | | |
| **Yes** | 366 (81.7%) | 543 (79.3%) | 1.16 (0.86, 1.58) | 0.99 (0.71, 1.39) |
| **No/Unknown** | 82 (18.3%) | 142 (20.7%) | *ref* | *ref* |
| **LTCF** in year prior** | | | | |
| **Yes** | 276 (61.6%) | 443 (64.7%) | 0.88 (0.69, 1.12) | 0.92 (0.64, 1.31) |
| **No/Unknown** | 172 (38.4%) | 242 (35.3%) | *ref* | *ref* |
| **Surgery in the Prior year** | | | | |

| | | | | |
|---|---|---|---|---|
| **Yes** | | | | |
| **no/unknown** | 145 (32.4%)<br>303 (67.6%) | 223 (32.5%)<br>462 (67.5%) | 0.99 (0.77, 1.28)<br>*ref* | 0.86 (0.66, 1.13)<br>*ref* |
| **LTACH*** in Year Prior** | | | | |
| **Yes** | 44 (9.8%) | 70 (10.2%) | 0.96 (0.64, 1.42) | 0.76 (0.49, 1.17) |
| **no/unknown** | 404 (90.2%) | 615 (89.8%) | *ref* | *ref* |
| | | | | |

*Controlling for Age, Sex, State, Race, ICU Stay in the prior 7 days, residence in the 4 days prior
**Long-Term Care Facility
***Long-Term Acute Care Hospital

| **Table 4: Time trends in Bactrim non-susceptibility among carbapenem-resistant *Acinetobacter baumannii* cases** | | |
|---|---|---|
| | cOR (95% CI) | aOR (95% CI)* |
| **Year (per one-year increase)** | 0.97 (0.92, 1.02) | 1.02 (0.96, 1.08) |
| **Sex** | | |
| **Male** | 1.13 (0.88, 1.46) | 1.12 (0.85, 1.46) |
| **Female** | *ref* | *ref* |
| **State** | | |
| **All other States** | *ref* | *ref* |
| **Georgia** | 1.86 (1.32, 2.62) | 2.02 (1.38, 2.96) |
| **Maryland** | 1.13 (0.79, 1.60) | 1.11 (0.77, 1.62) |
| **Age** | | |
| **0-49** | *ref* | *ref* |
| **50-64** | 0.90 (0.66, 1.23) | 0.92 (0.66, 1.28) |
| **65-79** | 0.84 (0.61, 1.15) | 0.84 (0.60, 1.18) |
| **80+** | 1.01 (0.68, 1.51) | 1.06 (0.69, 1.62) |
| **Race** | | |
| **Non-Black** | *ref* | *ref* |
| **Black** | 1.05 (0.82, 1.34) | 0.92 (0.71, 1.21) |
| **ICU Prior 7 days** | | |
| **Yes** | 1.45 (1.02, 2.05) | 1.16 (0.77, 1.75) |
| **No/Unknown** | *ref* | *ref* |

*Controlling for Age, Sex, State, Race, ICU Stay in the prior 7 days, residence in the 4 days prior

| **Table 5: Count and Percent of Bactrim non-susceptible CRAB cases by year** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2012 N= 114 Count (%) | 2013 N= 188 Count (%) | 2014 N= 160 Count (%) | 2015 N= 170 Count (%) | 2016 N= 117 Count (%) | 2017 N= 124 Count (%) | 2018 N= 121 Count (%) | 2019 N= 139 Count (%) |
| **Bactrim** | | | | | | | | |
| **Susceptible** | 58 (50.9%) | 113 (60.1%) | 109 (68.1%) | 98 (57.6%) | 64 (54.7%) | 82 (66.1%) | 75 (62.0%) | 86 (61.9%) |
| **Non-Susceptible** | 56 (49.1%) | 75 (39.9%) | 51 (31.9%) | 72 (42.4%) | 53 (45.3%) | 42 (33.9%) | 46 (38.0%) | 53 (38.1%) |