EVALUATION OF PATIENT RISK FACTORS FOR CARBAPENEM-RESISTANT ENTEROBACTERICEAE INFECTION

By

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To my mom and dad for the unending encouragement and countless hours of support through my university career

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LIST OF ABBREVIATIONS

ACF	Acute care facilities are a category assigned to acute care hospitals, clinics, and homecare.
ACH	Acute care hospital is a hospital with patient population that stays on average less than 14 days per admission.
BAL	Bronchoalveolar lavage is a procedure where a bronchoscope is passed through the nose or mouth and a small amount of fluid is squirted into the lung for specimen collection.
CRE	Carbapenem-resistant Enterobactericeae
KPC	*Klebsiella pneumoniae* carbapenemases
LTACH	Long-term acute care hospital is a hospital with patient population that stays an average of 14 or greater days per admission.
LTCF	Long-term care facilities are a category assigned to long-term care hospitals, skilled nursing facilities, or hospice care.
MRN	Medical record numbers are personalized identifiers a patient receives upon admission to UF Health Shands.
NDM	New Delhi metallo-beta-lactamase
OX-48	CRE producing OX48-like carbapenemases
VIM	Verona integron-encoded metallo-beta-lactamase

Abstract of Thesis Presented to the Graduate School
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Carbapenem-resistant Enterobacteriaceae (CRE) are a family of bacteria with high levels of resistance to many antimicrobials used in hospital settings today. We performed a retrospective chart review, from October 2014 to May 2016, in order to identify the risk factors contributing to CRE incidence among (i) cases versus controls, (ii) community acquired CRE infection and matched control infection, and (iii) hospital acquired CRE infection and matched control infection at UF Health Shands. The study consisted of 50 cases with positive CRE status and 100 controls with infections collected from similar anatomical sites as cases. Risk factors evaluated for significance were reasons for admission (planned versus emergency visit), antimicrobials, total length of stay, admitting location, discharge location, indwelling medical devices, and invasive procedures performed. Risk factors that were the most significant for cases versus controls were emergency admissions (OR 3.67; 95% CI 1.03-13.08), being administered inpatient medication (OR 5.88; 95% CI 2.27-15.24), admission from a long term care facility (Or 5.17; 95% CI 1.93-13.84), fluoroquinolone (OR 3.75; 95% CI 1.35-10.38), cephalosporin (OR 2.37; 95% CI 1.17-4.86), and invasive procedures with a scope (OR 4.57; 95% CI 1.31-16.02). Additional risk factors were significant for both

community-acquired cases and hospital-acquired cases. Significant risk factors were inserted into logistic regression to develop a model to identify patients best suited for CRE screening upon admission.

CHAPTER 1
GENERAL INFORMATION

Introduction

Carbapenem-resistant Enterobacteriaceae (CRE) are a family of bacteria contributing to the $20 billion in direct excess healthcare costs and 23,000 deaths from antibiotic resistant organisms each year[26]. The Enterobacteriaceae family includes many bacteria found in the human intestines, such as *Klebsiella* species and *Escherichia coli* [1]. CRE infections are rare in healthy individuals who do not have underlying health conditions, appearing mostly in individuals who reside within nursing homes, long-term care facilities, hospitals, and other health care settings[1]. CRE is mainly spread to new patients through contact transmission from an infected patient or healthcare worker[1]. These bacteria are opportunistic, entering the body through wounds or openings developed through the insertion of medical devices such intravenous catheters or urinary catheters[1]. CRE are therefore at the forefront of problems within our healthcare system, yet no definitive criteria have been identified for screening patients for CRE upon arrival at health care facilities. Most healthcare systems are less likely to view CRE as an emerging problem because it is difficult to evaluate trends due to the sporadic nature of cases[13]. Multiple factors must be observed ranging from admitting location, procedures undergone at the healthcare facility, comorbidities, and antibiotic regiments to determine the prevalence of CRE infections along with a viable screening process for CRE within healthcare systems[16].

Epidemiology

CRE is derived from plasmid-mediated resistance, which arises through the incorporation of an extrachromosomal piece of DNA that carries antibiotic resistance[37].

These resistance plasmids tend to be conjugative, allowing for direct cell-to-cell DNA transfer, which is how the carbapenem resistance plasmid gets transferred to a formerly susceptible bacterium [37]. Within the United States, there are five carbapenem resistance plasmids that can potentially be incorporated within bacteria, with the most prevalent of all of the CRE being *Klebsiella pneumoniae* carbapenemases (KPC).

KPC has become a problem in health care settings due to its ease of dissemination and limited antimicrobial treatment options[7]. There has been an increase in the last decade in the Carbapenem resistance reported in *Klebsiella* species, with one percent having resistance in 2000, increasing to around eight percent of Klebsiella having resistance in 2007[7]. KPC was first identified in the United States in North Carolina in 2001 and first became endemic in New York and New Jersey, with the first outbreak outside the United States occurring in Israel in 2004[7]. Through strain typing it was found that a single dominant strain (ST258) was responsible for the outbreaks in the United States, Israel, and later in India[7 38]. Since the initial outbreak in the United States, a few fit lineages have managed to spread across the globe and KPC is now present in most of the developed world and developing countries.

The next CRE is the New Delhi metallo-beta-lactamase (NDM) CRE, which was first identified in a case in New Delhi, India in 2007[2]. Since its discovery, NDM CRE has been reported on every continent except South America and Antarctica[2]. One of the first cases reported in the United States occurred in January, 2012, when a woman who travelled to Cambodia and was hospitalized with spinal cord compression in Ho Chi Min City, Vietnam[2]. Upon her return, she was immediately hospitalized with a diagnosis of lymphoma at her local hospital in Rhode Island and had a urine culture that was positive

for NDM CRE. During her stay on the hematology/oncology floor, it was found that one of the seven patients cohabitating the floor had also developed NDM CRE[2].

The plasmid carrying NDM has been found to be highly transmissible to other bacteria and lasts for prolonged periods within the infected host's gastrointestinal tract[2]. The recommendations to prevent spread that have been determined to be effective are high rates of hand hygiene, minimizing the use of invasive medical devices, and preventing unnecessary antimicrobial exposure by using a robust antimicrobial stewardship program[2]. Since identification of the first case in the United States in 2012, the NDM CRE has spread from the Northeastern US to all parts of the country with a total of 157 cases to date in the United States as of April 2016[2] (Figure 1-1).

Another CRE that is tracked within the United States is CRE producing OXA-48-like Carbapenemases (OXA-48). The OXA-48 CRE was first identified in Turkey in 2001[4]. The first case of OXA-48 in the United States occurred in 2009 but wasn't identified until 2012, using retrospective review of cases[4]. Of the 53 OXA-48 CRE identified by August, 2015, it was shown that a majority (81%) were *K. pneumoniae* isolates[4]. Among 35 patients who tested positive, those who provided an age during infection were found to have a median age of 70 years (range 29-91)[4]. Even with OXA-48 CRE occurring in clusters in the United States it is mostly believed to be contracted in patients who were admitted to health care facilities outside the US; 29 patients who tested positive provided travel histories and 19 (66%) had travelled internationally within the previous year of specimen collection[4]. Since April 2016, 61 cases of OXA-48 CRE have been identified within the United States[3] (Figure 1-2).

Another major CRE within the United States is Verona integron-encoded metallo-beta-lactamase (VIM) CRE. The VIM CRE belongs to the Class B metallo-β-lactamases group, which also contains another of the five main CRE, the IMP CRE, which has very few identified cases in the United States and globally[6]. The first reported case of VIM CRE within the United States was a women hospitalized after a Grecian cruise in July 2010[5]. Upon further testing of the strain obtained from this case, it was identified to be non-susceptible to all antimicrobials used to treat *Klebsiella*[5]. Of 22 patients that cohabitated the same medical floor as the women no other patients tested positive for CRE[5]. With only 17 cases, VIM CRE currently has the lowest prevalence within the United States[3] (Figure 1-3).

Health Care Settings

CRE has become an urgent problem within the health care system. Between 2008 and 2014, the detection of CRE has increased five-fold as reported by the CDC[8]. Within the United States CRE has so far been isolated in 48 of the 50 states, excluding Idaho and Maine. CRE is of large concern because of the complications caused and the death rates associated with CRE infections. In 2013, the CDC reported that 3.9% of short-stay acute care hospitals and 17.8% of long-term acute care hospitals had reported at least one health-care related CRE in the previous year[11]. A study done in a Northeast Ohio healthcare system found that 75% of CRE patients were transferred in from a long-term acute care hospital (LTACH), with only one of 13 patients being discharged home after infection[12]. In a meta-analysis done on 356 articles published about CRE, it was found that in seven studies that the death rate was 26% to 44%, and it was 3% to 4% in two studies done retrospectively[9]. Death rates were two times

higher in among patients who developed bacteremia with CRE as compared to those who had Carbapenem-sensitive Enterobacteriaceae (CSE)[9].

In Illinois, a study was performed looking at rates of transmission between health care settings, acute care hospitals (ACH) and LTACS, to evaluate the rates of CRE as well as the frequency of transfer between hospitals that causes CRE within the receiving hospital. LTACH were determined to play a central role in the distribution of CRE to other health care settings[10]. A hospital that shared four or more patients with an LTACH within a three-month period was found to have an elevated CRE rate[10]. Once the minimum four shared patients were found within an ACH, the crude CRE rate was doubled[10].

In a study conducted by Lee et al. measuring the prevalence of CRE with no organized control methods, unorganized control methods, and coordinated control methods, predicted nationwide prevalence of CRE would reach 11.1% with no organized control methods (Fig. 1)[8]. LTACH would see the greatest impact after ten years with the prevalence reaching 28.9%, with the least prevalence being observed in ACH at 3.1% with no control methods[8].

Antimicrobial Stewardship

Anti-microbial stewardship is another factor that is believed to play a role in CRE development and a helpful factor to identify patients for testing. Patients' antimicrobial histories have to be evaluated to see whether classifications of drugs, or combinations of drugs, are present in all patients testing positive for CRE. Limiting excess antimicrobial use along with ensuring the completion of an antimicrobial regiment has been seen to affect CRE infection rates[14]. In a case-control study of CRE, it was discovered that a history of fluoroquinolones and Carbapenems were more common

among patients testing positive for CRE[14]. This study also showed that 85% of patients who tested positive for CRE were previously treated with cephalosporin[14]. This study demonstrates the importance of considering antimicrobial treatment in the screening process for potential CRE patients.

Another key factor in the development of CRE is antimicrobials that allow pathogens to colonize the intestinal tract[15]. In a study of CRE infection rates in mice, antibiotics leading to suppression of anaerobic microflora and with limited activity against CRE-causing organisms were associated with the highest rates of CRE colonization[15]. The reverse was seen in mice with polymyxin E and gentamicin, which lead to suppression of CRE organism colonization[15].

Comorbidity

Lastly, comorbidities have been proven to be associated with an increased risk of CRE infections. The Charlson comorbidity index is used in studies to help determine underlying comorbidities of patients, determined by diagnostic codes found in administrative systems for each health care system[19]. A study analyzing 481 patients who tested positive for CRE identified that 415 patients had at least one comorbidity (91.4%), with a median Charlson comorbidity index of 2[20]. The most commonly reported comorbidity was diabetes (201 patients [44.3%]) followed by neurological disorders (185 patients [40.7%])[20]. Among the 185 patients with neurological disorders, 107 (57.8%) had an indwelling urinary catheter within two days of the positive culture, emphasizing the importance of this indwelling device in association with CRE[20].

In a case-control study of CRE risk factors performed using the Cumulative Illness Rating Scale (CIRS), an alternative to the Charlson comorbidity index, higher prevalence of comorbidities was identified in CRE positive cases as opposed to

controls[21]. Upon analysis of CIRS of 133 patients, it was found that comorbidities increased the risk for CRE infection among elderly patients with immuno-suppression or frail status[21]. High CIRS severity was also the main risk factor for CRE colonization among their study population (Odds Ration 13.3; 95% CI 6.88–25.93)[21].

These factors, along with others, need to be further evaluated in creating an effective surveillance system for the detection of CRE. Factors that influence development of CRE include comorbidities, procedures undergone, presence of indwelling devices during, co-infections with other resistant organisms, and length of stay. Determining the risk factors associated with CRE infection and colonization will allow health care systems to develop screening systems for CRE that are applicable to patients coming from the surrounding community and limit factors that increase the risk of CRE within the health care setting.

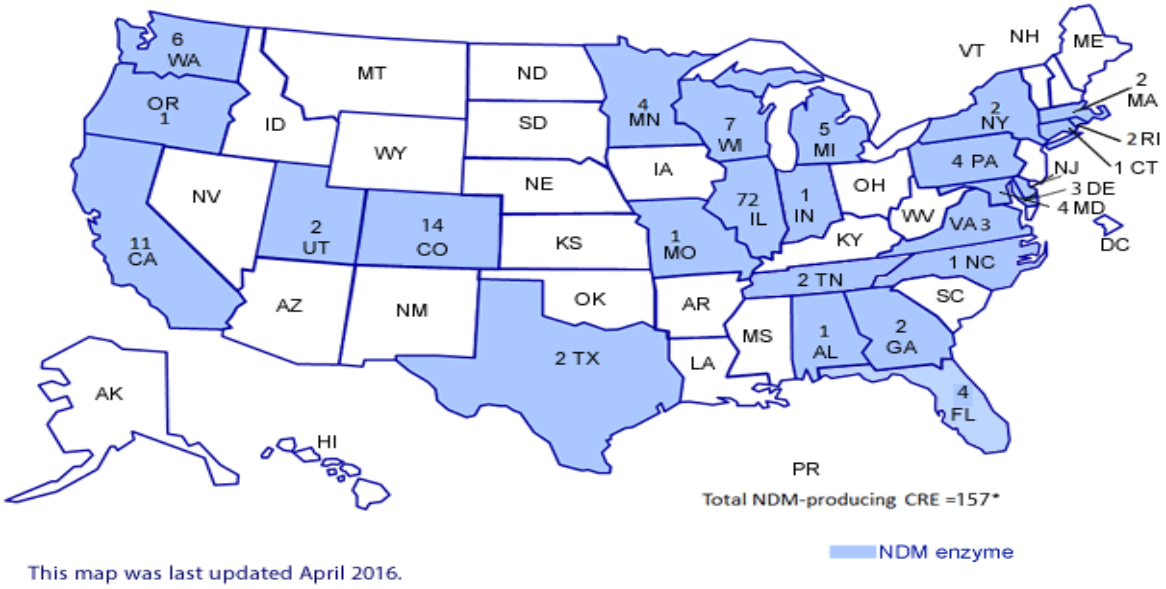

Figure 1-1. Patients with NDM CRE reported to the CDC as of April 2016[3]

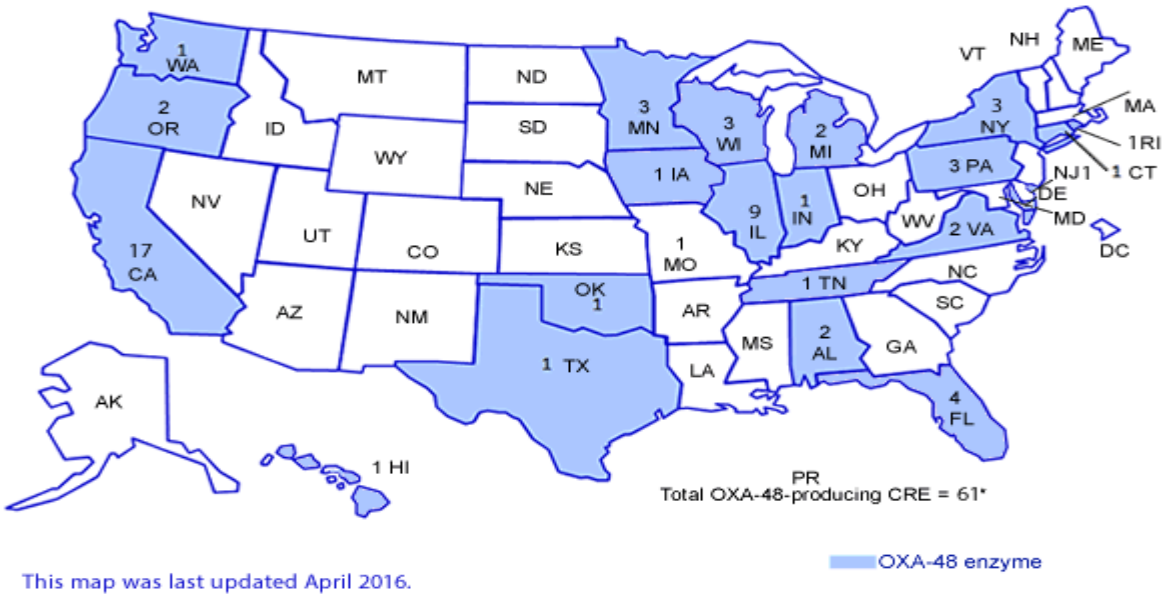

Figure 1-2. Patients with OX-48 CRE reported to the CDC as of April 2016[3]

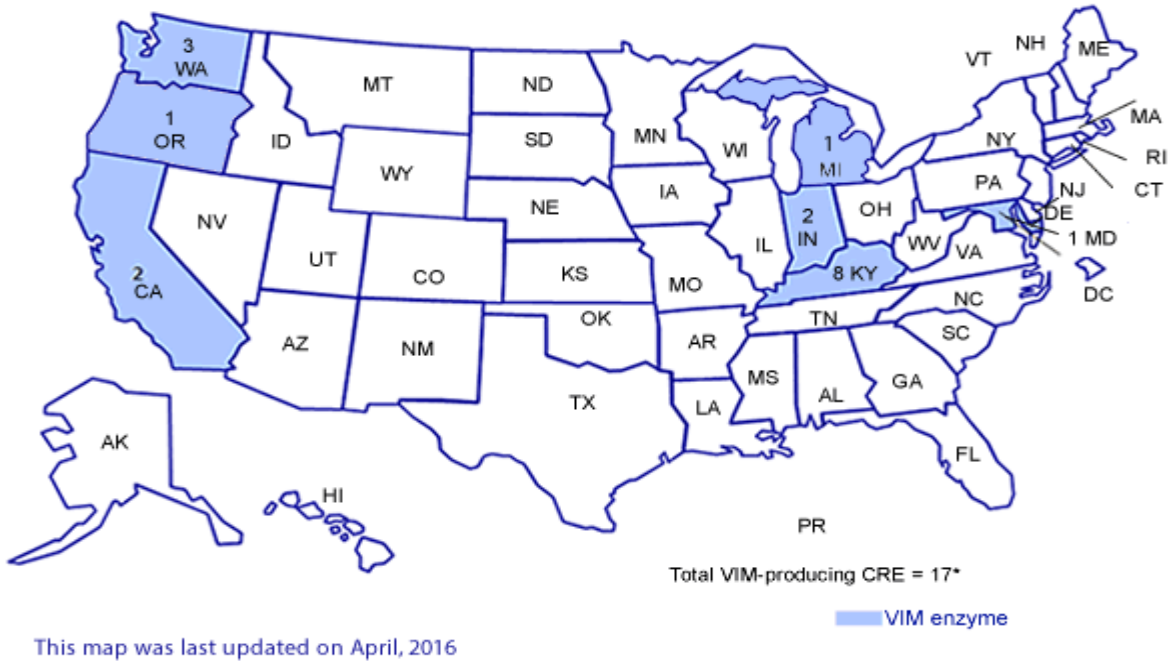

Figure 1-3. Patients with VIM CRE reported to the CDC as of April 2016[3]

CHAPTER 2
METHODS

Study Population

Risk factors of interest were identified using retrospective chart review. Cases were patients who had a positive culture for CRE at a UF Health Shands facility between October, 2014, and May, 2016. Controls were selected based on collection of any organism from a similar anatomical site within a date range of two weeks post or prior to the cases selection. Collection site and media of specimen were matched to that of the case infections. Cases and controls were identified using Theradoc® clinical services and controls were matched using a 1:2 ratio, resulting in 50 cases and 100 controls. All patient charts were viewed using EPIC USERWEB®.

Participants were excluded from the study based on predetermined criteria. Cases were required to be eighteen years of age at time of sample collection. Participants with fields not having an admitting date, collection date, or discharged date based on medical record coding were excluded from participation. Cases who had previous CRE infections as identified by EPIC outside the study window were excluded due to inability to match controls for these cases using Theradoc®.

Participants were evaluated on a case versus control basis and then further sub-analysis was performed. The sub-analyses were community-acquired CRE infections and matched control infections, and hospital-acquired CRE infections and matched control infections. Community-acquired infections were defined as having a positive sample collected prior to day three of stay during the admission. Hospital-acquired infections were considered any positive sample collected on day three or after upon admission.

Factors

Age

Age of cases was determined using birth date recorded upon admission to UF Health Shands during the admission that lead to a positive CRE infection status. Age of the controls was identified in the same manner using age upon positive CRE infection admission as the recorded age for the participant.

Age was then categorized as participants being under the age of 60 (Age <60) and equal to or over the age of 60 (Age ≥ 60). The age of 50 was selected as the dividing age due to 60 being the closest decade to the mean of the controls (mean=59.21).

Gender

Gender for cases was recorded as either female or male based on gender identified on admission that produced the positive CRE infection status. Gender for controls was recorded as either female or male based on gender identified on admission that produced the positive matched infection status.

Infection and Colonization

CRE status was categorized as infection or colonization for cases. Infection and colonization were distinguished by the site of the specimen collection. If the specimen was collected from within the body, such as blood cultures or bronchoalveolar lavage (BAL), it was considered to be an infection. Specimens collected from wounds, sputum, abscess drainage, or urine were considered to be colonization because they may not result in signs or symptoms. All specimens were categorized into four classifications; respiratory secretions, blood, urine, and wound/abscess drainage. Being in one of the four categories is not a determinant of being infection or colonization; in the respiratory

secretion category, a BAL was categorized as infection while sputum was classified as colonization.

Admitting Location

Both cases and controls were evaluated on the location they were most recently located in or admitted to prior to admission to UF Health Shands. All participants appeared from five possible locations. Participants who changed location within the recent past were still assigned an admission location based on most current location. An example is a participant who was discharged from the hospital to home on Jan. 1 and returned to the hospital on Jan. 3; this would still be counted as a home/residence admission due to spending any amount of time at another location.

Home/residence was assigned to any patient who was coming from their place of permanent residence. Traumatic events during every day activities, such as vehicle collisions or falls, are also under the home/residence admission label.

Participants were also admitted from acute care hospitals that were not affiliated with UF Health Shands. These are hospital systems that function similar to UF Health Shands and retain patients on average less than fourteen days.

Participants were also admitted from long-term care facilities (LTCF), which are settings in which patients remain greater than fourteen days during a single admission. LTCF consist of skilled nursing facilities, which are locations that maintain and care for an elderly population. LTCF also consist of hospice care facilities, which are locations that care for patients with terminal diagnosis and attempt control their pain symptoms for their remaining lifespan. Finally, participants were considered to be LTCF participants when they arrived from LTACH, which consists of patients who stay an average of fourteen days or greater.

The final admitting location of participants was rehabilitation facilities. Participants at rehabilitation facilities have typically been admitted from hospitals after an admission or surgery in attempt to regain function of senses or limbs. Examples are rehabilitation for lower limb weakness or speech therapy after a stroke.

Days until Positive Culture

The number of days until positive culture was identified by using date of admission of either case/control as initial event date (Day 1) and date specimen was collected as final event date. Dates were calculated using calendar days instead of 24-hour time periods. The first day of admission was calculated as day zero regardless of what time of day the patient was admitted. The same criteria were used when calculating specimen collection date.

Length of Stay

Total length of stay at UF Health Shands was calculated using date of admission of case/control to set event (Day 1) and release date as final event date. Similar to days until positive culture, calendar days were used instead of 24-hour time periods to calculated total days at UF Health Shands.

Total length of stay was categorized using the quartiles determined for the controls. The average of total length of stay was rounded to the nearest quartile and that quartile range was used as the reference group for comparison.

Total length of stay at UF Health Shands was also categorized into binary categories by using the average amount of days all controls had during their relevant infections as the reference. This was a ten-day average stay for controls.

Admitting Diagnosis

Admitting diagnosis was determined by the chief complaint participants reported upon admission. Participant complaints were reported both in the initial contact report along with final coding within H&P in the EPIC system. These two admissions reports were used to develop a comprehensive admission complaint.

After the admitting diagnosis was recorded, participants were separated into two categories; admissions for medical emergencies or trauma. Patients could be categorized as those with planned admittance, which was admission for pre-scheduled procedures. Patients could also be categorized as those with emergency admittance, which was those who arrived for trauma or medical emergencies Participants who experienced complications after procedures and were readmitted were categorized as emergency admission unless a planned readmission was stated in the medical record before discharge.

Total Hospital Admissions within Past Year

Total hospital admissions were calculated by using date of admission on which positive CRE or matching infection were identified as final date, and then observing previous admissions within the prior 365 days. Admissions were based on patient records as coded in EPIC. Patients who were only at the emergency department but not coded for admission did not have this UF Health Shands encounter counted as an admission. Patients who were transferred from an outside hospital to UF Health Shands had an admission added on to their total admissions in the past year even if the outside hospital admission was not recorded in the patient's EPIC record. Additional admissions at outside hospitals were not counted, as they could not be identified.

Indwelling Devices

Participants were evaluated for presence and total number of indwelling devices in place prior to a positive CRE infection or matching infection collection date. Devices were considered relevant to CRE infection or matching infection for controls if the device was present on the day of positive culture collection or the device was removed less than two days prior to culture collection, as per CDC criteria. The indwelling devices were as follows:

- Urethral Catheter
- GI Tube
- CVC Double Lumen
- CVC Triple Lumen
- PICC Double Lumen
- PICC Triple Lumen
- Arterial Line
- Hemodialysis Catheter
- Peripheral IV
- Graft or Fistula
- Colostomy
- Midline

CVC double lumen, CVC triple lumen, PICC double lumen, PICC Triple Lumen, and hemodialysis catheter were further grouped into central line devices.

Medication

Participants were evaluated for medication that was administered within the previous four weeks of positive CRE infection or matching control infection. Only antimicrobials were recorded. These consisted of all anti-bacterial, anti-viral, and anti-fungal medications. Participants' antimicrobials were averaged between determined means of antimicrobials by participant group. Antiviral medication or antifungal medications were categorized under those titles. Anti-bacterial medications were categorized into pharmaceutical classes due to multiple medications of the same class

being admitted over the duration of a participant's stay. Participant's medication was also recorded as extended if the participant was on any medication longer than fourteen consecutive days. All medications that were recorded during the study were categorized as one of the following pharmaceutical classes:

- Carbapenem
- Cyclic Lipid
- Fluoroquinolones
- Azithromycin
- Clarithromycin
- Imidazole
- Aminoglycoside
- Cephalosporins
- Glycopeptide
- Nitroimidazoles
- Antiviral
- Antifungal

Pharmaceutical classes were turned into a binary variable for evaluation using the mean number of antibiotics taken by controls during admission associated with infection. The average value of antibiotics rounded to the nearest whole number was three pharmaceutical classes of antibiotics taken during the admission.

Comorbidity and Comorbidity Scores

Participant's comorbidities were recorded based on the chart coding which was attached with a participant's admission. Comorbidities were identified as any secondary diagnosis within a participant's medical history that was not the primary diagnosis upon admission (ex. Metastatic tumor, HIV/AIDS, Diabetes). Comorbidities that were recorded from participants' charts were those that were identified by the Charlson Comorbidity Index in 1986 as well as the Charlson Comorbidity Index 2001 (CCI)[23 24]. The 2011 CCI was updated from the Charlson Comorbidity Index of 1986, based on the release of the ICD-10[23] 24. The recorded comorbidities were

- HIV/AIDS
- Cancer
- COP
- Dementia
- Diabetes
- Myocardial Infarction
- Metastatic Carcinoma
- Mild Liver Disease
- Moderate Liver Disease
- Paraplegia/Hemiplegia
- Peptic Ulcer Disease
- Peripheral Vascular Disease
- Renal Disease
- Rheumatologic Disease

Comorbidity score was determined by evaluating coded comorbidities based on both the CCI 1986 and the CCI 2011[23 24 25]. The CCI 1986 score took into account both comorbidities along with age, with every year over the age of 50 (years ≥50) adding a value of +1 per decade after. Comorbidities for both the CCI 1986 and the CCI 2011 were assigned values based upon already existing scoring charts for both CCIs[24 25].

The CCI is calculated during the end of a participant's stay at a health care setting. Participants arriving as trauma patients who were unable to be identified were unable to have a CCI associated due to lack of medical history.

Discharge Location

Discharge location is the physical setting a participant is released to after their discharge from UF Health Shands. The locations participants can be discharged to vary along with the level of care they receive at their discharge location vary. Participants discharged home are released to either self-care or home care with a health care professional coming in and providing assistance within their home or residence setting.

Participants are also discharged to long-term care facilities. These long-term care facilities include locations such as LTAC skilled nursing facilities, and hospice settings.

Participants discharged to these locations tend to be of a higher acuity and require ongoing care or devices such as ventilators.

Participants discharge to ACH and rehabilitation centers are transferred for reasons including proximity to home or residence, their long term physician's location, lessening of their acuity score to one a local hospital can provide care for, and recovery after surgery.

Participants transferred to rehab facilities have a lowered acuity and are discharged in order to regain function of limbs or learning to adapt to changes in limbs or body function.

Participants declared deceased do not get discharged but are still included in discharge locations for evaluation. Participants who died during their admission at UF Health Shands had their day of death considered the final day of the current admission.

Invasive Surgeries and Invasive Surgeries with Scopes

Invasive surgeries were obtained through data retrieval software using medical record codes. Each participant was evaluated individually a master list was created to ensure the invasive surgery occurred before date of positive culture collection.

Invasive procedures with scopes were also considered. These scopes were not differentiated by method or location of insertion. All invasive procedures with scopes performed on participants who had community-acquired infections were not counted towards a positive invasive procedure with scope.

Analysis

All data analysis was done using SAS 9.4 (SAS Institute, Cary, North Carolina). All values were considered significant with a p or T value of less than or equal to 0.05 (P/T value≤ 0.05). All odds ratios are presented within a 95% confidence interval (95%

CI) and were considered significant if the 95% CI does not contain the value of one. For any tables with cell counts less than five, significance values were evaluated using Fischer's Exact Test. Cell counts of zero or one were excluded from the analysis.

CHAPTER 3
RESULTS

Case and control data were analyzed on three different levels. The first analysis was between the cases and controls with no other factors used as exclusion criteria. The second analysis was looked at cases and controls who had community-acquired infections; these are infections that developed prior to hospitalization and that were identified within three days of admission. The third analysis included only cases and controls with hospital-acquired CRE infections.

Demographics

The study population was divided into 50 cases and 100 controls as based on our matching. The average age of cases was 58.9 years old and the average age of controls was 59.2 years old. The number of female cases was 22 (N=22) and the number of male cases was 28 (N=28). In the control group there were 45 females (N=45) and 55 males (N=55) (Table 3-1).

Looking at specimen type to determine infection or colonization (Table 3-2) shows there is no significant difference. Of the specimens that were considered infection among cases, we observed that there were 11 respiratory secretions (22% of all cases) and 7 blood specimens (14% of all cases). Of the specimens considered colonization, we observed that there were 16 urine samples (32% of all cases) and 16 wound/abscess drainage samples among the cases (32%of all cases). The averages of the Charlson comorbidity index did not prove to be significant, using both the criteria of the CCI 1987 and CCI 2011.

Cases vs. Controls

When we analyzed factors between cases and controls, all odds ratios were calculated by comparing the means of risk factors for CRE positive participants to the means of the controls rounded to the closest category (e.g. If the mean of previously resistant organisms for controls was 0.100 this was rounded to zero previously resistant organisms).

One significant factor that was observed between cases and controls was reasons for admission (Table 3-4). When observing the differences in participants admitted for emergency reasons versus those admitted for planned reasons, cases were 3.67 (95% CI 1.03-13.08) times more likely to have an unplanned, emergency admission than controls.

There was a significant difference between cases and controls with respect to amount of pharmaceuticals (counted by their subclass) (Table 3-5). Cases were 5.86 (95% CI 2.26-15.24) times more likely to have had inpatient antibiotics in the month prior compared to controls. Taking ambulatory antibiotics with no inpatient antibiotics in the month prior was not significant between cases and controls. The cases were 23.5 (95% CI 3.84-143.87) times more likely to take both inpatient and ambulatory antibiotics as compared to controls.

Admitting location was also a factor that proved to be significantly different between cases and controls. The binary variable (Table 3-6) of admission from a LTCF versus an ACF indicated that cases were 5.17 (95% CI 1.93-13.84) times more likely to be admitted from LTCF as opposed to controls. When admitting location was not binary (Table 3-7) the significant difference between cases and controls was admission from LTACH, with cases being 15.43 (95% CI 3.09-76.98) times more likely to be admitted

from LTCH as compared to controls. Cases are also 2.94 (95% CI 1.18-7.31) times more likely to come from ACH hospitals as compared to controls.

Discharge location was another factor observed on both the binary and individual level. On the binary level (Table 3-8); we saw that cases were 3.47 (95% CI 1.45-8.23) times more likely to be discharge to LTCF as opposed to controls. When observing the factors on an individual level (Table 3-9) cases were 6.67 (95% CI 1.22-36.95) times more likely to be discharged to hospice facilities as opposed to controls. Other significant discharge locations between cases and controls were LTCH (OR = 6.25, 95% CI 1.82-21.47) as well as skilled nursing (OR = 3.46, 95% CI 1.07-11.21).

Next, differences were noted for antimicrobials taken and the number of pharmaceutical class of antibiotics. Cases were compared to the average of the controls, which was 1.34, and the third quartile of the controls was three (75% of controls) which falls under the 0-3 binary antibiotics category. Cases were 4.24 (95% CI 1.75-10.24) times more likely to have taken more than three antibiotics in the past month as compared to the controls. When the antibiotics category was broken down into individual antibiotics, some antibiotics were significantly different between cases and controls. Cases were 3.75 (95 CI 1.354-10.38) times more likely to have taken Fluoroquinolones, 2.37 (95% CI 1.17-4.80) times more likely to have taken Cephalosporin, 5.44 (95% CI 1.02-29.14) times more likely to have taken Aminoglycosides (Table 3-10), and 5.41 (95% CI 1.35-21.95) times more likely to have taken carbapenems as controls were.

Cases were at increased risk versus controls to have had indwelling devices (Table 3-11). Cases with were 4.41 (95% CI 1.05-18.44) times as likely to have

colostomy bags as controls. Cases were also 13.5 (95% CI 1.58-115.50) times more likely to have a central line as compared to controls.

The final factor that had observed significance was invasive procedures performed with scopes (Table 3-12). Cases who had been scoped were 4.57 (95% CI 1.31-16.17) times more likely to have had a procedure performed with a scope as compared to controls. Invasive procedures performed without scopes were not found to be significant.

Other factors that were collected and were found to be not significant were age categorized (Table 3-13), Charlson Comorbidity Index both 1987 and 2011. Previous infection or colonization with resistant organisms also was not significant at the level of cases and controls.

Community Acquired CRE

Participants were then analyzed at the level of community-acquired infections of CRE and the subsequent matched control infection. Community acquired infections were defined as patients having a positive sample collected on the day of admission or within two days after. After excluding the hospital-acquired cases, there were 84 participants with community-acquired infections. Of these participants, 23 were cases. There were 10 females and 13 males and an average age of 56.09 years. The controls consisted of 61 participants with 28 females and 33 males and an average age of 57.34 years.

Community acquired cases differed from controls with respect to inpatient and ambulatory antibiotics taken (Table 3-14). Cases were 10.15 (95% CI 2.80-36.88) times more likely to have taken inpatient antibiotics compared to controls. Cases were also

27.5 (95% CI 3.98-190.04) times as likely to have both inpatient and ambulatory antibiotics.

For location of admission, both binary and individual locations had significant differences between community-acquired cases and controls. Using binary admission locations (Table 3-15), cases were 4.99 (95% CI 1.39-17.84) times more likely to be admitted from a LTCF as opposed to controls. Investigating individual admission locations (Table 3-16), cases were 18 (95% CI 1.81-178.81) times more likely to be admitted from a LTCH as opposed to controls. The remaining admission locations were not significant between cases and controls.

Along with location of admission, some antibiotics had significant differences between cases and controls among participants (Table 3-17). Cases were 3.82 (95% CI 1.36-10.73) times more likely to have taken nitroimidazoles as compared to controls. The other significant antibiotics taken were Fluoroquinolones, with cases being 26.69 (3.06-232.89) times more likely to have taken Fluoroquinolones in the month prior as compared to controls.

The last significant factors within the community acquired CRE infections were indwelling devices (Table 3-18). Of the indwelling medical devices observed, only urethral catheters proved to have a significant difference among community-acquired CRE infection. Cases were 4.495 (95% CI 1.57-15.65) times more likely to have a urethral catheter within two days prior up to date of positive culture collection as compared to controls.

The factors that were not significant among the community-acquired infections were CCI 1987 and 2011, age categorized (Table3-19), and all indwelling devices.

Hospital-Acquired CRE

Within our population, 66 participants had CRE infection and/or colonization attributed to hospital acquisition. Samples were considered hospital-acquired if they were collected any time after the third day of admission. The factors significant for these participants will differ from the community-acquired infections due to different exposures and environment.

The first significant factor was total length of stay between cases and controls (Table 3-19). The second quartile was established as the reference during analysis because this was the quartile closest to the mean of the hospital control infections total length of stay. Cases were 11.46 (95% CI 1.25-104.60) times as likely to stay between 15 and 34 days, and 19.83 (95% CI 1.29-171.83) times as likely to stay 35 days or greater as compared to controls. When total length of stay was made into a binary variable, (Table 3-21) 14 days was used as the dividing day total for the categories. Cases were 18.08 (95% CI 2.22-147.10) times more likely to stay greater than 14 days as compared to controls.

Location where participants were admitted from was significant for participants admitted from LTCH (Table 3-22). Cases were 16.2 (95% CI 1.73-151.85) times more likely to be admitted from LTCHs as compared to controls. When locations of admission were made binary based on being LTCF, cases were 6.48 (95% CIi 1.23-34.16) times more likely to be admitted from a LTCF compared to controls (Table 3-23).

There was also a significant difference observed for discharge location (Table 3-24). Cases were 14.4 (95% CI 1.38-155.24) times more likely to be discharged to a LTCH compared to controls. A similar trend was seen when discharge locations were

made binary (Table 3-25). Cases were 3.18 (95% CI 1.14-8.92) times more likely to be discharge to a LTCF compared to controls.

Antibiotics showed no significance among cases and controls (Table 3-26). When antibiotics were categorized as greater or less than the control average of antibiotics during admission (antibiotics ≤ 3), cases were 3.10 (95% CI 1.07-8.94) times more likely to have had greater than three antibiotics in the last month.

The final significant factor that followed the same trend as the comparison at the case versus control level was that of invasive procedures with the use of a scope (Table 3-27). Invasive procedures performed without scopes were not significant between the hospital-acquired infections. Analyzing invasive surgeries performed with scopes, cases were 5.05 (95% CI 1.20-21.29) times more likely to have an invasive procedure performed with a scope compared to the controls.

Indwelling medical device presence was not significant between cases and controls (Table 3-28), nor was age categorized (Table 3-29).

Table 3-1. Demographics of Total Population

	Controls	Cases
Total N	100	50
Age	59.21	58.92
Gender		
Male	55	28
Female	45	22
Charlson Comorbidity Index (CCI)		
CCI 1987	4.3	4.72
CCI 2011	2.72	3.14

Table 3-2. Infection and Colonization by Community or Hospital Acquired Cases

	Community or Hospital		
	Community	Hospital	Total
Infection	11	19	30
Colonization	12	8	20
Total	46	54	100

Table 3-3. Infection and Colonization by Category for Cases

	Community or Hospital		
	Community	Hospital	Total
Respiratory Secretion	3	8	11
Blood	3	4	7
Urine	10	6	16
Wound/ Abscess Fluid	7	9	16
Total	23	27	50

Table 3-4. Odds Ratio Emergency versus planned admissions

Effect	Point Estimate	95% Wald Confidence Limits	
Admission Reason: Emergency vs Planned	3.674	1.032	13.077

Table 3-5. Odds ratios Inpatient and Ambulatory Antibiotics

Effect	Point Estimate	95% Wald Confidence Limits	
Inpatient Antibiotics	5.875	2.265	15.241
Ambulatory Antibiotics	5.222	0.721	37.85
Both Inpatient and Ambulatory Antibiotics	23.5	3.839	143.867

Table 3-6. Odds ratios admission from LTCF versus ACF

Effect	Point Estimate	95% Confidence Limits Confidence Limits	
LTCF vs ACF	5.167	1.928	13.842

Table 3-7. Odds ratios individual admitting location

Effect	Point Estimate	95% Wald Confidence Limits	
ACH vs. Home	2.939	1.181	7.312
Corrections vs Home	>999.999	<0.001	>999.999
Hospice vs Home	3.429	0.206	57.183
LTCH vs Home	15.429	3.092	76.988
Skilled Nursing Home vs Home	3.429	0.789	14.892
Clinic vs Home	1.714	0.148	19.849
Rehab vs Home	3.429	0.206	57.183

Table 3-8. Odds ratios discharge to LTCF versus ACF

Effect	Point Estimate	95% Wald Confidence Limits	
LTCF versus ACF	3.468	1.452	8.283

Table 3-9. Odds ratios individual discharge location

Effect	Point Estimate	95% Wald Confidence Limits	
ACH vs Home/Residence	2	0.321	12.463
Death vs Home/Residence	3.333	0.996	11.154
Homecare vs Home/Residence	1.579	0.464	5.376
Hospice vs Home/Residence	6.667	1.215	36.593
LTCH vs Home/Residence	6.25	1.819	21.469
Rehab vs Home/Residence	4	0.853	18.752
Skilled Nursing vs Home/Residence	3.461	1.069	11.21

Table 3-10. Odds Ratio Antibiotics and Antibiotics Binary

Effect	Point Estimate	95% Wald Confidence Limits	
Fluoroquinolones	3.747	1.353	10.379
Cephalosporins	2.373	1.172	4.804
Nitroimidazole	1.714	0.787	3.734
Glycopeptides	1.857	0.931	3.703
Aminoglycosides	5.444	1.017	29.136
Cyclic Lipopeptide	1	0.177	5.654
Carbapenems	5.406	1.332	21.951
Erythromycin	4.125	0.365	46.625
Antibiotics ≥ 3 versus Antibiotics ≤ 3	4.235	1.751	10.243

Table 3-11. Odds Ratio Indwelling Devices

Effect	Point Estimate	95% Wald Confidence Limits	
Colostomy	4.409	1.054	18.442
Central Lines	13.5	1.578	115.498
Arterial Line	0.762	0.309	1.876
Urethral Catheter	1.325	0.638	2.749
Hemodialysis Graft Fist	3.128	0.505	19.355

Table 3-12. Odds Ratio Invasive Procedure & Invasive Procedures with Scope

Effect	Point Estimate	95% Wald Confidence Limits	
Invasive Procedures	1.657	0.805	3.411
Invasive Procedures w/ Scope	4.571	1.305	16.017

Table 3-13. Odds Ratio Age

Effect	Point Estimate	95% Wald Confidence Limits	
Age ≥ 60	0.887	0.449	1.751

Table 3-14. Odds Ratio Inpatient and Ambulatory Antibiotics (Community Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Inpatient Antibiotics	10.154	2.796	36.875
Ambulatory Antibiotics	7.333	0.933	57.611
Inpatient and Ambulatory Antibiotics	27.5	3.979	190.04

Table 3-15. Odds Ratio Binary Admission Location (Community Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
LTCF vs. ACF	4.900	1.369	17.536

Table 3-16. Odds Ratio Individual Admitting Location (Community Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
ACH vs Home	3.75	0.953	14.764
Hospice vs Home	4.5	0.259	78.204
LTCH vs Home	18	1.812	178.808
Nursing Home vs Home	4.5	0.789	25.659
Rehab vs Home	4.5	0.259	78.204

Table 3-17. Odds Ration Antibiotics taken in Prior Month (Community Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Nitroimidazole	1.966	0.501	7.72
Cephalosporins	3.819	1.36	10.727
Fluoroquinolones	26.250	3.007	229.133
Glycopeptide	2.72	0.911	8.118
Cyclic Lipopeptide	2.725	0.163	45.473
Antibiotics ≥ 3 versus Antibiotics ≤ 3	8.998	0.885	91.461

Table 3-18. Odds Ratios Indwelling Devices (Community Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Urethral Catheter	4.959	1.571	15.653
Colostomy	8.998	0.885	91.461
Arterial Lines	2.81	0.372	21.227

Table 3-19. Odds Ratio Age (Community Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Age ≥ 60	1.258	0.479	3.303

Table 3-20. Odds Ratio Total Length of Stay (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Total Length of Stay Quartile 1	<0.001	<0.001	>999.999
Total Length of Stay Quartile 3	11.455	1.254	104.601
Total Length of Stay Quartile 4	19.833	2.289	171.832

Table 3-21. Odds Ratio Total Length of Stay Binary (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Total Length of Stay Greater than 14 days	18.079	2.222	147.101

Table 3-22. Odds Ratio Admission Location (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
ACH	2.7	0.798	9.139
LTCH	16.2	1.728	151.85
Skilled Nursing Facility	2.7	0.154	47.392

Table 3-23. Odds Ratio Admission Location Binary (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Admission LTCF versus ACF	6.475	1.228	34.155

Table 3-24. Odds Ratio Discharge Locations (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
ACH	2.25	0.111	45.722
Death	5.625	0.537	58.909
Homecare	3.6	0.257	50.33
Hospice	9	0.522	155.241
LTCH	14.4	1.375	150.807
Rehab	13.5	0.878	207.622
Skilled Nursing Facility	11.25	0.972	130.22

Table 3-25. Odds Ratio Discharge Location Binary (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Discharge LTCF versus ACF	3.181	1.135	8.918

Table 3-26. Odds Ratio Antibiotics Taken in Prior Month (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Aminoglycosides	2.312	0.359	14.876
Glycopeptide	0.952	0.344	2.637
Nitroimidazole	1.228	0.448	3.366
Cephalosporins	0.8	0.217	2.946
Fluoroquinolones	0.957	0.242	3.774
Cyclic Lipopeptide	0.462	0.045	4.69
Carbapenems	3.6	0.811	15.97
Erythromycin	3.04	0.262	35.332
Antibiotics ≥ 3 versus Antibiotics ≤ 3	3.095	1.072	8.938

Table 3-27. Odds Ratio Invasive Procedure & Invasive Procedures with Scope (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Invasive Procedures	1.055	0.362	3.077
Invasive Procedures w/ Scope	5.051	1.199	21.289

Table 3-28. Odds Ratio Indwelling Devices (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Hemodialysis Graft/Fistula	2.312	0.359	14.876
Arterial Line	0.333	0.11	1.006
Urethral Catheter	0.361	0.128	1.02
Central Line	2.035	0.72	5.751
Colostomy	2.312	0.359	14.876

Table 3-29. Odds Ratio Age (Hospital Acquired)

Effect	Point Estimate	95% Wald Confidence Limits	
Age ≥ 60	0.686	0.252	1.872

CHAPTER 4
DISCUSSION AND CONCLUSION

Discussion

Significant risk factors were identified at all levels that were observed. More risk factors were observed at the most inclusive level of all cases and controls. Fewer risk factors were identified as significant in the sub analysis of community-acquired cases and hospital-acquired cases.

Plan versus Emergency Admissions

Patients with CRE were 3.674 times more likely to present to UF Health Shands for emergency reasons, such as medical emergencies and traumas, compared to patients without CRE infections. These findings have not been previously reported in literature, this could result from the categories being very broad making them not as applicable within the screening process. Further research can be done into the types of planned admittance (e.g. transplants, and chemotherapy) and emergency admissions (e.g. feinting, and skull fracture).

Ambulatory and/or Inpatient Antibiotics

Taking antibiotics in an ambulatory manner, outside of UF Health Shands, or taking antibiotics on an inpatient basis was a significant risk factor. There was an increased risk for being on inpatient antibiotics for both cases versus controls and the community-acquired CRE cases. CRE-infected participants were 5.875 times more likely to have taken inpatient antibiotics on the case versus control level, and 10.154 times more likely to have taken inpatient medication on the community-acquired level. Taking only inpatient antibiotics among community-acquired cases would result from antibiotics administered upon arrival or antibiotics given within the first two days of stay.

Cases were also 23.5 times as likely to take inpatient and ambulatory medication on the case versus control level, and cases were 27.5 times as likely to take inpatient and ambulatory medication on the community acquired level. Taking both inpatient and ambulatory antibiotics results from use of antibiotics before admission and either continuance of antibiotics or being administered new antibiotics during the participant's admission. Patients who present with these risk factors are potentially those most suited for CRE screening. In a recent study done by Marchiam et al., antibiotic exposure in the three months prior to colonization was observed, and they discovered that there is an increased risk of 11.4 (2-64.3) for cases of CRE (n=91) compared to those without CRE[14].

Admitting Location

Admission location was a significant risk factor for our participants at all three levels of evaluation. On the binary level of admission from a LTCF, those participants who developed hospital-acquired CRE had the highest risk from this factor. This could be due to colonization of CRE at these LTCFs and not being screened upon admission to UF Health Shands, creating increased incidence within hospital-acquired CRE category, which with screening would have been attributed to the outside community. When the admitting locations were separated out of their binary categories, we observed only one admitting location to be significant among all three categories. All cases, both community and hospital-acquired admission, were at increased risk of developing CRE infection if participants were admitted from a long-term acute care hospital. In a study by Marguez et al., similar findings were found regarding LTACH and ACH rates, with their study showing incidence of 2.54 per 1000 patient days at LTACH as compared to 0.31 per 1000 patient days at ACH[35].

Discharge location

Along with admitting locations, results show there is increased risk of CRE-infected patients being discharge to certain discharge locations. Looking at the binary variable of being discharged to LTCF, this was an increased risk for CRE-infected participants on the case versus control level and for those with hospital-acquired CRE infections. When observing all participants, cases were 3.468 times more likely to be discharged to a LTCF, and hospital acquired cases were 3.181 times more likely to be discharge to the LTCF. When discharge locations were looked at by individual locations, cases were at an increased risk of being discharged to hospice facilities, skilled nursing facilities, and LTACH (OR=6.67, OR=3.401, and OR=6.25 respectively). Hospital-acquired cases only had a significant increased risk of being discharge to LTACH (OR 14.4). A study by Lee et al. highlighted the importance of coordinating and controlling transfer and discharge locations of CRE-infected patients. The authors reported that with coordinated regional control of the transferring of patients, they averted 21.3% of CRE infections compared to an uncoordinated effort[8]. This demonstrates the need for discharge to locations equipped to accommodate CRE-infected patients and the need for avoidance of health care settings not equipped to handle these CRE infections.

Antibiotics

Antibiotics were the next risk factor found to be significant on two levels of analysis. Multiple individual antibiotics were found to be significant in at least one level of analysis. Comparing cases to the controls, the participants with positive CRE infections were at greater risk for fluoroquinolone, cephalosporin, carbapenem, and aminoglycosides (OR=3.747, OR=2.373, and OR=5.444 respectively). Significance of individual antibiotics was also observed on the community-acquired case level. Cases

were at increased risk of having been administered cephalosporin and fluoroquinolone (OR=3.819 and OR=26.687 respectively). In a study conducted by Schechner et al., fluoroquinolone was determined to be a predictor for CRE renal carriage, as it was on our case versus control and community-acquired levels, with an OR of 4.27 (95% CI 1.10-16.6)[28]. These positive samples were collected from a different anatomical site but do demonstrate fluoroquinolone being a predictor for CRE infection. In another study by Gasink et al., similar results were found when observing fluoroquinolone and the development of KPC-producing *K. pneumoniae*, with an increased OR of 3.39 (95% CI 1.118-7.66) in a study with fifty-six cases and 863 controls[29]. The last significant risk factor among the case versus control level and community-acquired level was cephalosporin; cases were 2.373 times more likely to take cephalosporins as compared to controls on the case versus control level, and 3.819 times as likely on the community-acquired level. In the article by Gasink et al., which identified fluoroquinolone use as a predictor, they also found within the same population that cephalosporin had an OR of 2.55 (95% CI 1.18-5.52)[29].

The antibiotics that were found to have significance only when all cases and controls were observed were carbapenem and aminoglycoside. In one study evaluating whether the proper antimicrobial course was followed for CRE positive patients, eight of the 16 (50%) patients had received carbapenems[30]. Carbapenem administration, in that study and among our participants, may be attributed to not knowing patient's CRE status at time of administration. The final antibiotics that showed significance on the case control level were aminoglycosides. This is not unexpected within a CRE-positive population because aminoglycosides are often administered to treat CRE infections.

Since the 1950s, aminoglycosides have been preferred to colistin, with both being known as “drugs of last resort”[11].

When the average number of antibiotics for CRE positive participants was compared to that of the controls, there was a significant difference. The average number of antibiotics taken by controls in the last month was three or fewer; cases were 8.998 times more likely to take greater than the average number of antibiotics for controls. Physicians could be contributing to this risk factor by not following best antimicrobial stewardship recommendations or overprescribing medications. Our CRE-positive participants may also have had underlying conditions that were being treated along with the CRE infection, which would result in increased antibiotic usage. However, this is not very likely due to similar comorbidity scores indicating the populations were in similar health.

Indwelling Devices

Indwelling devices were found to be significant on the cases versus controls level as well as the community-acquired level. On the case versus control level, we observed that cases were 4.41 times as likely to have had a colostomy and 13.5 times as likely to have had a central line compared to controls. The finding of increased risk of CRE with colostomy is interesting because there is not much research looking into the association. In a study conducted by Chang et al., they observed 51 participants (17 with carbapenem resistance and 34 without) and they identified that none of their carbapenem-resistant group had colostomies compared to three with carbapenem sensitivity[31]. Our results were in contrast of these findings, potentially due to a small sample size or difference in population demographic by Chang et al.[31].

Cases were also 13.5 times more likely to have had a central line compared to controls on the case versus control level. Articles have been published on single cases of possible CRE infection acquired through central lines but little research has been conducted looking at large populations and their risk of CRE development[32].

On the community-acquired level, having a urethral catheter was an increased risk factor for CRE infection, with cases being 4.96 times more likely to have a urethral catheter as compared to controls. In a study by Huang et al. observing carbapenem-resistant *Acinetobacter baumannii* bacteremia, Foley catheters were identified as a significant risk factor and were found to be present in 83.9% of carbapenem-resistant *Acinetobacter baumannii* patients and 65.2% of carbapenem-susceptible *Acinetobacter baumannii* patients[36].

Invasive Procedures/ with Scope

The last observed factor was invasive procedures performed on participants prior to collection of positive CRE bacteria sample. Among all levels of analysis, there was no significant difference when all invasive procedures were compared between cases and controls. When only invasive procedures with scopes were observed, we saw significance on the case versus control level as well as the hospital-acquired participants. Cases were 4.571 times as likely to have had an invasive procedure with a scope as compared to a control. Cases with hospital-acquired infections were 5.051 times as likely to have had invasive procedures with scopes as compared to their controls. We were not able to adequately analyze community invasive procedures and those with scopes due to the low number of procedures. In a 2013 outbreak in Chicago, a side-viewing duondenoscope (ERCP) was found to be responsible for infection and

colonization of 38 patients[33]. These devices pose a risk due to the challenging nature of cleaning the devices and accessibility to all parts of these devices[33].

Limitations

Even with significant findings among all cases and controls, community-acquired CRE infections, and hospital acquired CRE infections, there were limitations to the study. Limitations included the size of the study population, coding of the electronic medical records (EMR) in Epic, and the lack of knowledge of past medical records. The total amount of cases was limited by the timeline of TheraDoc, the software used to identify cases, being available at UF Health Shands. This left us with a relatively small N (N=50). The limited population size lead to very large confidence intervals, which do not allow for an evaluation of the significance of the impact of the risk factor on the outcome of CRE development. With the limited population size, some risk factors on the sub-levels of analysis, community-acquired and hospital-acquire infections, did not allow for references for comparison. This occurred in cases of admitting location where there was only one participant admitted from a correction facility so no conclusions could be drawn for the significance of this admitting location.

The coding of the medical records was the next limitation encountered during the study. All EMRs were coded by UF Health Shands employees after the participant had been discharged and was to be billed for the admission. There is potential for variance in coding between various employees. All information recoded was verified to the best extent possible by the researcher, but discrepancies arose due to coder oversight. Errors occurred mostly in admitting locations, with locations such as home and ACH being cited as admitting location during the same admission with evidence for both locations being found throughout the EMR. There was not enough evidence to disprove

either location so as the location that was identified in the History and Physical note at time of admission was designated as the admitting location.

The last limitation of the study arose due to the lack of past medical history or EMR of patients being admitted from other health care facilities or having visited an outside healthcare facility in the past calendar month. This limitation mostly affected antibiotic counts, indwelling devices, and past invasive procedures. Counts for any of the risk factors could have been affected by the availability of these medical records, but due to the inability to acquire the records they were omitted and significance was determined on the medical information contained within the current EMR at UF Health Shands.

Applications of Findings

Identifying the significant risk factors for CRE infection allows us to create possible models to identify the best individuals to be screened upon admission. Using the determined risk factors, two models will be developed to screen individuals; one for those who are admitted from the community with little known past medical history and the second for patients arriving with a known past medical history.

The first model would be applied to patients arriving with little known past medical history. This would include a quick verbal interview, visual cues upon arrival, and limited to no available EMR. To develop the algorithm, significant risk factors would be evaluated within a logarithmic regression to identify a score ($\hat{Y}$) which could be used to determine best fit for screening. The significant risk factors are drawn from the community-acquired infections because these patients arrived to UF Health Shands and have a positive sample of CRE bacteria or matching infection prior to day three of admission, with minimal opportunity for hospital procedures or interventions. The risk

factors used within the algorithm are antibiotics taken ambulatory (AMB) and/or inpatient (IP), arriving from a LTCF, having taken fluoroquinolones in the prior month, and having a urethral catheter (Figure 4-1). All variables within the model are binary; in terms of urethral catheter, if the patient was admitted with a urethral catheter then the patient would have a one (1) inserted in the algorithm. Stepwise logistic regression was used to determine the risk factors that are of significance within the logistic regression model.

The second algorithm will be for patients admitted with a known past medical history. This would include verbal interview, visual cues, EMR, and all past medical records from UF Health Shands and other health care settings admissions. The significant factors for this algorithm are drawn from all participants at the case versus control level of analysis. The significant factors for the algorithm are emergency versus planned admission, antibiotics taken ambulatory (AMB) and/or inpatient (IP), arriving from a LTCF, having taken fluoroquinolones in the prior month, having taken cephalosporin in the prior month, having taken aminoglycoside in the prior month, taking greater than three antibiotics, having a colostomy, and having an invasive procedure performed with a scope device (IPS) (Figure 4-2). Stepwise logistic regression was used to determine the risk factors that are of significance within the logistic regression model.

Future research can build on the study presented, with two goals. The first goal would be to identify more risk factors for CRE infection and to expand the two models proposed above to be more specific. Risk factors such can be evaluated at a more precise level, invasive surgery with scopes risk factor the type of scope procedure can

be observed (e.g. ERCP, colonoscopy, endoscopy). Emergency and planned admission can be looked at more precisely, with planned admissions being separated into reason for planned admission and emergencies being separated by severity (e.g. fever >103 versus skull fracture).

A second goal of future research would be to identify the validity of the models produced from this study. To conduct this research, all patients admitted during a set time period or until a certain participant population is reached which can be determined through a SAS 9.4 power test (SAS Institute, Cary, North Carolina). All samples collected would be tested for CRE infection or colonization, and, separately from the CRE testing, the models (Figure 4-1 and Figure 4-2) would be applied to patients to determine a score based on these models. Then all positive CRE samples would be matched with the patients and their model score would be averaged to create a threshold score. This threshold score would serve as a baseline at which, if a patient arriving has a higher model score, they would be selected for CRE screening.

In conclusion, multiple risk factors of CRE infection were recorded through the course of this study. Not all risk factors proved to be significant with regard to CRE infection but a few factors did pose an increased risk to the development of a CRE infection or colonization. These factors lead to the development of models which could be applied to identify patients most suited for CRE screening. There are many more risk factors that may contribute to the development of CRE infection, but this study revealed risk factors for this specific patient population which can be built upon to create a more specific model in the future.

$$\hat{Y} = (-2.6839) + (2.0145)(\text{Urethral Catheter}) + (2.2919)(\text{Fluoroquinolone}) + (1.9527)(\text{IP}) + (1.5914)(\text{AMB}) + (3.1635)(\text{Both IP and AMB})$$

Figure 4-1. Algorithm for Patients Arriving with Little Known Medical History

$$\hat{Y} = -2.6839 + (2.1012)(\text{LTCF}) + 1.7385)(\text{IP}) + (2.2785)(\text{AMB}) + (3.6321)(\text{AMB and IP}) + (1.5533)(\text{Colostomy}) + 1.4557)(\text{IPS})$$

Figure 4-2. Algorithm for Patients Arriving with Known Medical History

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BIOGRAPHICAL SKETCH

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