

**EMERGING WAVES OF CARBAPENEM RESISTANCE AMONG GRAM NEGATIVE
PATHOGENS AT A TERTIARY CENTER**

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ABSTRACT

Carbapenem resistant organisms (CROs) have emerged as a public health crisis because of high rates of mortality and morbidity. Epidemiologic and clinical factors contributing to patient outcomes vary. Objectives included evaluating emergence of CROs, and identifying factors associated with patient mortality at UPMC Presbyterian hospital. Microbiology records were extracted from the most common gram-negative pathogens, *E.coli*(Ecol), *Klebsiella pneumoniae*(Klpn), *Pseudomonas aeruginosa*(Psar), *Enterobacter aerogenes/cloacae*(Entb), *Serratia marcescens*(Serm), and *Acinetobacter baumannii*(Acat) from 2000-2015.

We identified 84,597 isolates from 37,823 patients. Among all isolates 9.5% (8,864) were classified as CROs. Standardized by patient, 7.5% of isolates were CR in 2000, 14.6% in 2015 ($P<0.001$). Among all CROs Psar-58%, Klpn-17%, Acat-12%, Ent-7%, Ecol-4%, and Serm-2%. Psar accounted for 86% of CROs in 2000 but only 55% in 2015 ($P<0.0001$). Conversely, Acat, Klpn, and Ent increased from 1-4% CR isolates, to 9%, 19%, and 15%, respectively ($P<0.0001$ for each). Psar was the most common CR pathogen annually. Various CROs emerged as second most common (Acat, 2010; Klpn, 2012; Ent, 2014). Recurrence rates at 90-days were highest for Psar(23%), and lowest for Ecol(3%, $P<0.001$). Carbapenem daily defined doses (DDD's)/1,000 patient days increased over the study ($P<0.001$); other antibiotic doses did not change. By cross-correlation analysis, carbapenem DDDs correlated with emergence of CROs at zero-lag time

interval ($R^2=0.90$, $P<0.001$), indicating that increased consumption and emergence of CROs occurred simultaneously.

CROs were identified from 4,994 patients; mean age was 57.8 years, 56% were men, 41% were ICU residents, and 26% were solid-organ-transplant(SOT) recipients. Mortality rates at 30-d and 90-d were 19% and 32%, respectively. Rates at 30-d were higher for Acat(28%, $P<0.001$), lower for Psar(17%, $P<0.001$). Rates ranged by culture site from 27% (blood) to 12% (urine, $P<0.001$). Age (OR=1.02, 95% CI:1.016-1.026, $P<0.001$) and ICU residence (OR=3.63, 95% CI:3.10-4.26, $P<0.001$) were independent predictors of 30d mortality. SOT recipients had lower mortality rates($P<0.001$). A prediction model was constructed to estimate 30d mortality risk. CROs emerged in waves at our center, but were not associated with increased carbapenem usage. CROs are associated with high mortality rates. Prediction models may be useful for clinician evaluation and reduction of this public health burden.

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PREFACE

I would like express my gratitude to the members of my committee which included Dr.'s Nancy N. Glynn, Jeremy J. Martinson, and Ryan K. Shields for their mentorship throughout this process. I would like to acknowledge Lloyd Clarke for his mentorship as well as his extensive efforts in collection, analysis, and interpretation of the data used in this study. Additionally, I would like to acknowledge Melissa Saul and the EMPI support team for their assistance with this project.

1.0 INTRODUCTION

Antimicrobial resistance has emerged as a healthcare crisis around the world. The World Health Organization (WHO) defines antimicrobial resistance (AMR) as the ability of a microorganism, like bacteria, to prevent an antimicrobial, such as antibiotics, from working against it (WHO, 2016). When bacteria develop non-susceptibility to at least one agent within three or more categories of antimicrobials, they are classified as Multidrug-Resistant Organisms (MDROs) (Magiorakos et al., 2012).

The rising prevalence of MDROs is an increasing public health threat according to the Centers for Disease and Control (CDC, 2009a). Increasing rates of MDROs are a result of excessive and inappropriate antimicrobial use (Chaisathaphol & Chayakulkeeree, 2014), (Tuon, Gortz, & Rocha, 2012), (Tun et al., 2016), (Brotfain et al., 2016). Carbapenems are a class of antibiotics that exhibit a broad antimicrobial spectrum and stability against common antimicrobial resistance mechanisms. Accordingly, carbapenems have been increasingly utilized for the treatment of MDROs. As one of the last lines of defense, bacterial resistance to the carbapenems presents a detrimental problem to public health. Given the lack of remaining treatment options, carbapenem resistant organisms (CROs) are associated with disproportionately high rates of mortality and morbidity (Tian et al., 2016), (Judd, Ratliff, Hickson, Stephens, & Kennedy, 2016).

Despite the recent trends in antimicrobial resistance, the epidemiology of CROs remains poorly defined at individual centers. Patient and hospital factors associated with the emergence of CROs are not well defined either. At the University of Pittsburgh Medical Center (UPMC)

Presbyterian hospital, carbapenem resistance has been identified across many common Gram-negative bacteria. The impact that each of these Gram-negative pathogens has on patient outcomes as well as the overall burden of CROs at UPMC is unknown. Therefore, it was the goal of this study to evaluate the most common Gram-negative pathogens at UPMC Presbyterian and to gain an understanding of the extent of carbapenem resistance. Clinical laboratory results from the past 16 years were evaluated to define the epidemiology of CROs, identify associations with antibiotic use and CROs, and describe the characteristics and outcomes of patients with CROs.

1.1 EPIDEMIOLOGY OF CARBAPENEM RESISTANT ORGANISMS

1.1.1 Antimicrobial Resistance

Antimicrobials like antibiotics, antivirals, and antifungals have been used to treat infections since the 1940's. Over the past seventy-five years, treatment of infections has reduced infection-related illness and death (CDC, 2016a). However, the cumulative toll of antimicrobial use has provided microorganisms with the opportunity to adapt, resulting in reduced effectiveness. According to the CDC, every year at least 2 million people are infected with antibiotic resistant organisms, and more than 23,000 people die from these infections (CDC, 2016a).

Antimicrobial resistance can develop over time naturally due to genetic mutations or changes. However, antimicrobial resistance can also be amplified by the misuse or overuse of antimicrobials. Some examples of antibiotic misuse includes the use of antibiotics in animals to promote growth, underuse by patients such as stopping prior to the completion of an antibiotic, or misuse such as using antibiotics to treat a viral infection such as the flu (WHO, 2016). A study evaluating the relationship of antibiotic consumption and Gram-negative rod (GNR) hospital

acquired infections (HAIs) by Chen et al. showed that CR-*Acinetobacter spp.* was driven by broad spectrum antibiotic consumption (Chen et al., 2013).

Another factor that contributes to the acceleration of AMR is the ability of antimicrobial resistant-microbes to spread from person to person. Infection control measures are often implemented to prevent the spread of AMR in the health care setting, but improper use of personal protective equipment and inadequate use of proper hand hygiene allows these organisms to prosper (Bartsch et al., 2016), (Carroll, Rangaiahagari, Musabeyezu, Singer, & Ogbuagu, 2016).

Moreover, patients are now at the highest risk for development of AMR as ever before. The increasing frequency of MDROs isolation in the hospital coupled with growing at-risk populations (older age, critically-ill, immunosuppressed) provides ample opportunity for AMR to flourish. Furthermore, the emergence of new resistance mechanisms threatens our ability to treat the most common infectious diseases. Taken together, without effective antimicrobials, modern medical advancements could be mitigated by AMR. For instance, organ transplantation and other complex surgeries are not possible without effective antimicrobial therapies to prevent infection.

1.1.2 Carbapenem Resistance

Carbapenems are a class of broad spectrum, beta-lactam antibiotics. Among the beta-lactams, carbapenems are known to have the broadest spectrum against both Gram-positive and Gram-negative bacteria. Additionally, they are stable against many common mechanisms of resistance. It is for these reasons that carbapenems are considered a last resort or last line of defense in treatment of resistant organisms (Papp-Wallace, Endimiani, Taracila, & Bonomo, 2011).

Unfortunately, the recent emergence of CROs has been shown in several studies resulting in increased resistance to carbapenems around the world (Gaibani et al., 2014), (Gopalakrishnan &

Sureshkumar, 2010), (Chouchani, Marrakchi, & El Salabi, 2011). Carbapenem resistance has been noted among various Gram-negative pathogens (Heudorf et al., 2016). At our center, the most common Gram-negative pathogens include *Enterobacteriaceae* (*E. coli*, *K. pneumoniae*, *E. cloacae*, *E. aerogenes*, *S. marcescens*), *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. These organisms account for a significant portion of HAIs.

1.1.3 Carbapenem Resistant *Enterobacteriaceae*

Enterobacteriaceae are a family of Gram-negative, bacilli or rod-shaped bacteria that are responsible for almost half of all nosocomial infections annually in the United States. The most frequently reported species of *Enterobacteriaceae* include *Escherichia*, *Klebsiella*, *Enterobacter*, *Proteus*, *Providencia*, and *Serratia* (Miller-Keane, 2003).

Enterobacteriaceae are components of the normal bacteria in the human microbiome. Once these organisms develop resistance to carbapenems, they are considered carbapenem resistant *Enterobacteriaceae* or CRE. CRE infections do not typically occur in healthy individuals. They are more common among hospitalized patients or individuals who reside in nursing homes or frequent healthcare clinics. Those with compromised immune systems, open wounds, or invasive devices are more likely to develop CRE infections. Infections with such organisms are extremely deadly, and have been reported to cause death in some 50% of all patients infected (CDC, 2016b).

1.1.4 *Acinetobacter baumannii*

Acinetobacter is a Gram-negative bacterium that is most commonly found in soil and water. Though there are many species of *Acinetobacter*, the most prominent species is

Acinetobacter baumannii. *A. baumannii* accounts for about 80% of all reported *Acinetobacter* infections (CDC, 2010).

Similar to CRE, infection with *A. baumannii* is not a threat to healthy individuals. Hospitalized patients with weakened immune systems, open wounds, or indwelling medical devices are susceptible to *A. baumannii* infection. Transmission occurs in susceptible persons by means of person to person contact or contact with contaminated surfaces (CDC, 2010). Therefore, implementation of infection control measures is the best way to reduce the spread of this organism.

Treatment of *A. baumannii* is typically chosen on a case by case basis. It is very important to consider underlying diseases and the patient's current health prior to choosing treatment of this infection. Additionally, when treating *A. baumannii* it is important to consider this organism's ability rapidly acquire resistance to antimicrobials (Pragasam et al., 2016), (Hsu et al., 2017). The overall limited treatment options for CR-*A. baumannii* are associated with high rates of mortality and poor patient outcomes.

1.1.5 Pseudomonas aeruginosa

Pseudomonas is a Gram-negative bacteria found widespread in the environment. The most common species is *Pseudomonas aeruginosa* (CDC, 2014). Serious infection caused by *P. aeruginosa* is most common in hospitalized patients, especially those with weakened immune systems. This infection in a critically ill patient can cause serious disease and even lead to death. At our center, CR-*P. aeruginosa* is more common than CRE (Buehrle et al., 2016).

Similar to the aforementioned pathogens, once this organism develops resistance to carbapenems it is extremely hard to treat. Like *A. baumannii*, *P. aeruginosa* is able to rapidly acquire antimicrobial resistance; however, the organism also exhibits intrinsic resistance to many classes of antibiotics, which makes it even harder to treat (Gang & Jie, 2016). Therefore, infection

control measures are important in the prevention of *P. aeruginosa*. This organism can be spread by person to person contact as well as contact with a contaminated surface. Hand hygiene as well as personal protective equipment like gowns and gloves should be utilized to prevent spread of this disease.

1.2 INCIDENCE AND PREVALENCE

The prevalence of MDROs is dependent upon several factors. The CDC has shown that the prevalence of MDROs can vary by time, location, healthcare setting, and level of care (CDC, 2009b; Jonathan R. Edwards, Margaret A. Dudeck, & Atlanta, 2006). Several studies have shown that ICUs, especially those within a tertiary center have higher prevalence than non-ICUs (Kollef, 2001), (Zilahi, Artigas, & Martin-Loeches, 2016). The National Nosocomial Infection Surveillance (NNIS) report published in 2006 showed that prevalence of MDROs in the United States has increased steadily over the several preceding decades (Jonathan R. Edwards et al., 2006)

Prior to 1992, CRE were not common in the United States. Data from the National Healthcare Safety Network (NHSN) showed an increase in resistant isolates among *Klebsiella*, and *Escherichia* in the early 2000's. CRE is the cause of many HAIs. The CDC requires state health departments to complete surveillance of many types of HAIs including infections caused by CRE. It is through these reports that we are able to gain a better understanding of the incidence and prevalence of CRE. The CDC defines CRE as “resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possess a carbapenemase”. Prevalence of CRE has increased over the past ten years through the dissemination of *Klebsiella pneumoniae* carbapenemase (KPC) (Won et al., 2011). According to the CDC, patients with KPC-producing CRE have been identified in every state except for two in the U.S. as of February 2016. In

response, state and regionally-based approaches have been implemented to effectively decrease the incidence of CRE (Centers for Disease & Prevention, 2013).

MDR *Acinetobacter baumannii* is rarely found in the community setting. The prevalence in the healthcare setting, however, has increased over the last decade [CDC 2016 Multidrug-Resistant *Acinetobacter baumannii*]. The epidemiology of MDR *A. baumannii* is rather complex, and it is often the reason that this pathogen is difficult to control. Although the data may not be generalizable for the population, various studies have been completed to evaluate the incidence and prevalence of CROs. One study evaluated various publications to show an incidence of MDR *Acat* to be 0.14 (95% CI, 0.136-0.161) per 1,000 patient days at risk [Nelson RE et. al. 2016].

MDR-*P. aeruginosa* is the most common resistant pathogen [NNIS 2004, Fernandez-Barat 2016]. In 2012, a study was completed to evaluate the epidemiology of MDR- and CR-*P. aeruginosa* in children, and the results showed an increased prevalence of MDR- and CR-*P. aeruginosa* in this patient population [Logan et al 2012]. Another study completed in 2016 showed that *P. aeruginosa* is the most common cause of ICU-acquired pneumonia, and a high prevalence of MDR is seen within this population [Fernandez-Barat 2016].

1.3 RISK FACTORS

Many studies have been completed over the last decade to evaluate risk factors for MDROs and CROs. One prominent finding in the literature is best stated by Chaisathaphol and Chayakulkeeree from their study in 2014: “the strongest risk factor for acquiring MDR Gram-negative infection was previous antibiotic use” (Chaisathaphol & Chayakulkeeree, 2014). Various other studies support this statement that prior antibiotic use is a risk factor for MDROs, and ICU admission as well as age >65 were common risk factors among these studies (Brotfain et al., 2016;

Tun et al., 2016; Tuon et al., 2012). A study in 2016 on MDR- *A. baumannii* showed that age >65, chronic obstructive pulmonary disease, and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score higher than 20 were all independent risk factors (Brotfain et al., 2016). Similarly, other research supports that critically ill patients have an increased risk of developing CROs. Furthermore, having a solid organ transplant is a risk factor for many infectious diseases including but not limited to bacteremia, sepsis, pneumonia, and urinary tract infections (Donnelly et al., 2016), (Lalueza et al., 2016). Another study from 2012 showed that admission to an ICU, higher leukocyte counts, and previous carbapenem use were statistically associated with *CR-P. aeruginosa* (Tuon et al., 2016). Although the risk factors are typically evaluated by type of pathogen causing the infection, it is evident that many risk factors overlap.

1.4 TREATMENT

Treatment of MDROs is extremely difficult and ever-changing as these organisms evolve. Carbapenems are commonly used to treat infections caused by MDROs. However, the overuse of carbapenems over time is thought to have contributed to the development of CROs (Tuon et al., 2016).

1.4.1 Treatment Options and Outcomes

Treatment of CROs varies widely from center to center as each center attempts to best treat their patient population. Moreover, treatment options for CROs have evolved over time. Initial treatment of CROs was with the use of a single antibiotic, which is referred to as monotherapy. Unfortunately, most medications used to treat CROs individually were toxic salvage agents like

aminoglycosides, polymyxins, and tigecycline. Regardless of treatment choice, there were concerns for efficacy, increasing resistance, and toxicities (van Duin, Kaye, Neuner, & Bonomo, 2013). Due to poor response rates of monotherapy, the use of antibiotic combinations to treat CROs has become the new standard. Combination regimens typically include a carbapenem in combination with one or more salvage agents. Most recently, however, new agents have been developed with activity against CROs, highlighting a new era in treatment of CROs. The most recently approved antibiotic for the treatment of CRE is a combination drug called Ceftazidime-Avibactam. It was approved in the United States in 2015. Although the drug appears to be a safe and effective treatment option, resistance to this antibiotic has already been documented in the United States (Shields et al., 2016).

Other treatment options for these patients involve investigational drugs, there are three primary groups working to gain FDA approval. Carbavance® is one of the antibiotics currently pursuing FDA approval. It is a drug being produced by The Medicines Company. Carbavance® is a combination therapy that uses an already existing carbapenem called Meropenem in combination with Vaborbactam. Data suggest that Carbavance® is effective for the treatment of CRE causing complicated Urinary Tract Infection (cUTI) (Wire, 2016). Additionally, a phase three study is well underway for the use of Carbavance® to treat complicated Intra-abdominal Infection (cIAI), bacteremia, and both Healthcare-Associated and Ventilator-Associated Bacterial Pneumonia(HABP/VABP). It is estimated to hit the market as early as 2017.

Shionagi is a company working to develop S-649266. This drug is a cephalosporin that is being used in investigational studies for the treatment of carbapenem resistant gram-negative pathogens (CRGNP) causing cUTI, sepsis/bacteremia, HABP, and VABP. Enrollment for the phase 3 study began in 2016.

Plazomicin® is the third antibiotic currently being tested through clinical trials. Achaogen is the company developing this drug. Similar to the two aforementioned antibiotics, Plazomicin is being developed for the treatment of CRE causing cUTI, sepsis/bacteremia, HABP, and VABP.

Overall, the development of new antibiotics that are effective at treating CROs and well tolerated is novel. Treatment has improved over time, and it continues in that direction as the demand for such antibiotics increases. Nevertheless, the emergence of further resistance upon the introduction of these agents into the clinic suggests that AMR will be a continuing problem. Understanding the epidemiology of CROs at individual centers will allow detection of trends and an attempt to prevent further spread of these organisms.

There is large push for new treatment options as the prevalence of these organisms continues to increase. Resistance to all available antibiotics is a growing concern. However, the need for treatment options cannot wait for these results as current treatments are associated with overall poor outcomes (van Duin et al., 2013).

1.5 PUBLIC HEALTH SIGNIFICANCE

CROs are associated with higher rates of mortality and morbidity than those with susceptible strains (CDC, 2013). In addition to mortality rates, extended length of hospitalization as well as increased hospital costs are large public health concerns.

The CDC has deemed CRE to be a global threat as of 2013. CRE along with other antibiotic resistant organisms are reaching extremely high levels around the world. Antimicrobial resistance has been identified in every region of the world (WHO, 2016). There is a global need to change the way in which antibiotics are used and prescribed. Additionally, there is a global need for implementation of infection control programs and new treatment options.

Every year in the United States at least 23,000 deaths occur from infections caused by antibiotic resistant organisms. More than \$30 billion is spent on treating these drug-resistant infections annually (CDC, 2013). The economic burden of CRE was further evaluated by Bartsch et al. in 2016. They found that the median cost of a single CRE infection can range from \$22,484-\$66,031 for hospitals, \$10,440-\$31,621 for third-party payers, and \$37,778-\$83,512 for society (Bartsch et al., 2016). They also found that the annual cost of CRE outweighs the annual cost of many other chronic and acute diseases. Another study estimated the costs for MDR *A. baumannii* to range from \$33,510- \$129,917 per infection (Nelson et al., 2016).

Although MDR pathogens are typically associated with nosocomial infections, the prevalence of these organisms in the community is increasing (van Duin & Paterson, 2016). Various studies have shown the spread of MDR pathogens from procedures such as hemodialysis, bronchoscopies, and gastroscopies (Bajolet et al., 2013; Vincenti et al., 2014). This type of transmission has provided different risk factors than nosocomial infections of these organisms, and occurrence has even been noted among healthy individuals (van Duin & Paterson, 2016).

Despite recent global trends, the epidemiology of CROs at individual centers remains poorly defined. Patient and hospital factors associated with the emergence of CROs are also unclear at this time. Various studies have been completed, but the data lacked power due to the small sample sizes or short time frames that were evaluated. Gaining a site-specific impact of these organisms can help identify where continued antibiotic management and infection control efforts should be focused. Additionally, understanding individual site impact of CROs could help illustrate the deafening need for new treatment options and reduce the public health burden of this burgeoning problem.

2.0 OBJECTIVES

Similar to many other centers in the US, previously susceptible Gram-negative pathogens have been identified as carbapenem-resistant at UPMC Presbyterian. However, the overall burden and epidemiology of CROs is unknown. Therefore, we evaluated CROs among the most common Gram-negative pathogens at this tertiary center. The primary objective of the study was to define the epidemiology of CROs over a 16-year period. To achieve the primary objective, our specific aims included defining the incidence of CROs at UPMC Presbyterian, identifying associations between trends in antibiotic use and the emergence of CROs, and further describing characteristics and outcomes of patients with CROs.

The hypotheses of this study were:

H1: Carbapenem resistance has emerged over time across many pathogens at UPMC Presbyterian hospital.

H2: Increased carbapenem usage is associated with increasing rates of CROs at UPMC Presbyterian hospital.

H3: Patient outcomes vary by pathogen, severity of illness, and underlying diseases.

3.0 METHODS

3.1 ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) at the University of Pittsburgh. The IRB waived the need for written informed consent from participants due to the nature of the study. The study was a retrospective observational study that involved very minimal risk to subjects involved in the research, intentional deception of participants was not involved, nor did the research involve a vulnerable population. The waiver provided for subjects does not have any adverse effects on the right and welfare of the subjects involved.

3.2 HOSPITAL SETTING AND DEFINITIONS

UPMC Presbyterian Hospital is a tertiary center located in Pittsburgh, Pennsylvania with 792 licensed beds. Intensive care units (ICUs) account for more than 15% (122) of all beds. UPMC Presbyterian's specialties include cardiology, gastroenterology, neurosurgery, organ transplantation, and trauma.

The MISYS-SUNQUEST Laboratory Information System at UPMC was used to extract clinical microbiology data as well as demographic information throughout the study, and no changes were made to the system during the study timeframe (2000-2015). The medical archival

system (MARS) data repository was utilized for underlying conditions such as transplant status. Antibiotic exposure data was extracted the UPMC pharmacy data warehouse, and antibiotic daily defined doses (DDDs) were calculated based on the methods and conversion standard that the WHO Collaborating Center for Drug Statistics Methodology has created. Specifically, DDDs are a unit of measurement that represents the average daily dose of a drug used (WHO-CCDSM, 2016). Utilizing DDDs provides a standardization of antibiotic consumption across centers. Additionally, DDDs enable researchers to identify trends in drug use over time in different settings. At UPMC Presbyterian, the DDD calculation was based on patient charge data. The number of units is calculated over time for each antibiotic using the WHO DDD conversion formula. This value is standardized by 1,000 patient days.

Only isolates that were tested for carbapenem susceptibility were included in these analyses. A unique patient was identified by the patient's first CR-pathogen. Recurrence was defined as isolation of another CRO pathogen after 90 days from the index case had lapsed. For pathogen-specific analysis, patients were re-included in more than one CRO was identified. For outcome analysis, patients were included only once and classified according to the first CRO recovered. Patient records were linked to the Social Security Death Index (SSDI) to determine time from CRO culture to death.

3.3 BACTERIAL ISOLATES

Isolates were identified by the UPMC clinical microbiology laboratory using standard methods. Only isolates collected from patients in the hospital were included; isolates collected from patients in outpatient locations were excluded from data analysis. Susceptibility testing was performed by Kirby-bauer disc diffusion and/or standard automated methods (Microscan). Results

were interpreted using the most recent Clinical and Laboratory Standards Institute (CLSI) definitions shown in Tables 1-3 (CLSI, 2015). We defined CROs as any targeted pathogen demonstrating non-susceptibility (Intermediate or Resistance interpretation) to any carbapenem.

Table 1. CLSI 2015 carbapenem defined breakpoints *Enterobacteriaceae*

Antimicrobial Agent	Zone Diameter Interpretive Criteria (nearest whole mm)			MIC interpretive Criteria ($\mu\text{g/mL}$)		
	S	I	R	S	I	R
Doripenem	≥ 23	20-22	≤ 19	≤ 1	2	≥ 4
Ertapenem	≥ 22	19-21	≤ 18	≤ 0.5	1	≥ 2
Imipenem	≥ 23	20-22	≤ 19	≤ 1	2	≥ 4
Meropenem	≥ 23	20-22	≤ 19	≤ 1	2	≥ 4

^a. Breakpoints are defined as susceptible (S), intermediate (I), or resistant (R).

Table 2. CLSI 2015 carbapenem defined breakpoints *Pseudomonas aeruginosa*

Antimicrobial Agent	Zone Diameter Interpretive Criteria (nearest whole mm)			MIC interpretive Criteria ($\mu\text{g/mL}$)		
	S	I	R	S	I	R
Doripenem	≥ 19	16-18	≤ 15	≤ 2	4	≥ 8
Imipenem	≥ 19	16-18	≤ 15	≤ 2	4	≥ 8
Meropenem	≥ 19	16-18	≤ 15	≤ 2	4	≥ 8

^a. Breakpoints are defined as susceptible (S), intermediate (I), or resistant (R).

Table 3. CLSI 2015 carbapenem defined breakpoints *Acinetobacter spp.*

Antimicrobial Agent	Zone Diameter Interpretive Criteria (nearest whole mm)			MIC interpretive Criteria ($\mu\text{g/mL}$)		
	S	I	R	S	I	R
Doripenem	≥ 18	15-17	≤ 14	≤ 2	4	≥ 8
Imipenem	≥ 22	19-21	≤ 18	≤ 2	4	≥ 8
Meropenem	≥ 18	15-17	≤ 14	≤ 2	4	≥ 8

^a. Breakpoints are defined as susceptible (S), intermediate (I), or resistant (R).

3.4 STATISTICAL ANALYSES

Incidence rates were calculated as the total number of pathogen specific CROs per 1000 patient days. Linear regression was used to compare carbapenem resistance and antibiotic DDDs over time. Time series, cross correlation regression analysis was used to determine rates of CROs as a function of DDDs. Rates of 30- and 90-day mortality were determined from time of first CRO isolation. Kaplan-Meier curves were used to plot survival over time. The curves were compared by log-rank test among CROs.

Chi-square tests were used in univariate analysis to identify predictors of death. Continuous and categorical variables were compared by student's t-test and chi-square respectively. The factors tested included age, gender, location, culture source, and organism.

In multivariate analysis, a logistic regression model was built with stepwise backward selection procedures using variables with a p-value $<.10$. Using beta-coefficients from the logistic regression model, a prediction equation was derived by fitting the data to an inverse probability equation. Area under the curve (AUC) was evaluated using a receiver operating characteristic (ROC) curve.

4.0 RESULTS

4.1 EPIDEMIOLOGY OF CROs AT UPMC

Among targeted pathogens, 84,597 isolates from 37,823 unique patients were identified during the study period (Figure 1). *E. coli* was most common, followed by *P. aeruginosa* and *K. pneumoniae*. Overall, 9.5% (8,864/84,597) of isolates were classified as CR (Figure 2). Rates of resistance were highest for *P. aeruginosa* and lowest for *E. coli*. *P. aeruginosa* accounted for 58% of all targeted CROs.

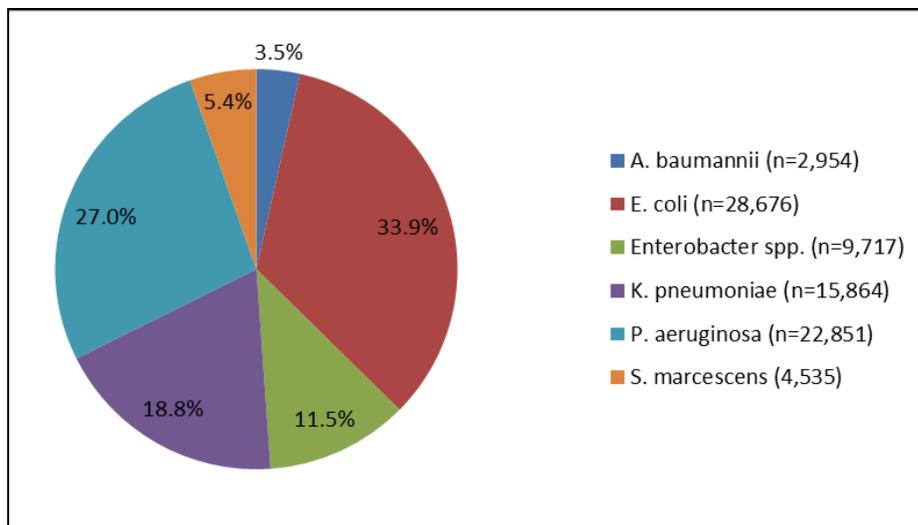


Figure 1. Gram-negative pathogens at UPMC Presbyterian (n=84,597)

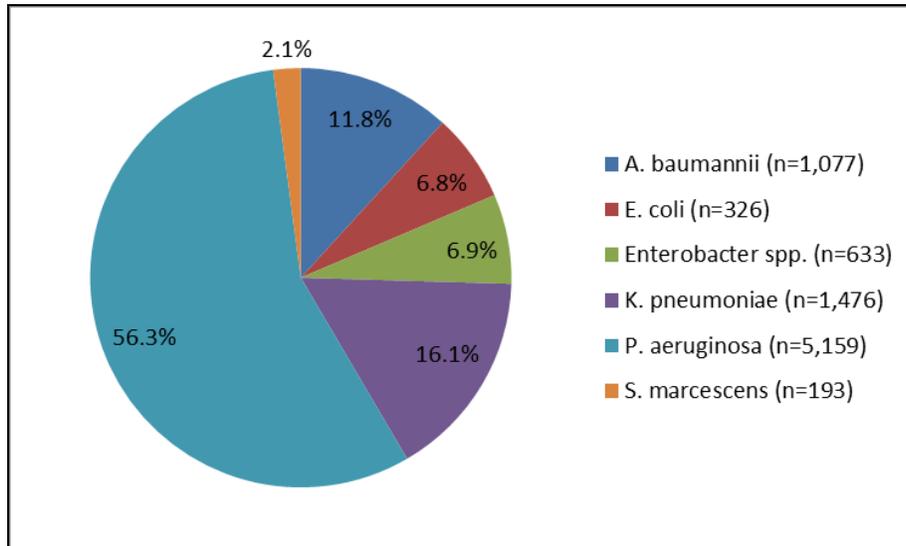


Figure 2. Carbapenem resistant pathogens at UPMC Presbyterian (n=8,864)

The proportion of isolates that were CR increased significantly from 2000 to 2015 ($P<0.001$). A significant increase in CR was also noted from 2000-2015 among Acat, Ent, and Klpn isolates ($P<0.0001$). Conversely, CR among Psar isolates decreased significantly over the study duration ($P<0.0001$) (Table 4).

Table 4. Carbapenem Resistance Rates per 1,000 Patient Days - UPMC Presbyterian 2000-2015

Pathogen	n	Rate of Carbapenem-resistant Pathogens per 1,000 Patient Days															
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
A. baumannii	1,077	0.04	0.04	0.04	0.05	0.02	0.05	0.07	0.19	0.32	0.36	0.39	0.34	0.2	0.18	0.2	0.19
E. coli	326	0.00	0.00	0.00	0.02	0.03	0.04	0.05	0.05	0.08	0.07	0.07	0.1	0.14	0.2	0.11	0.12
Enterobacter	633	0.03	0.05	0.02	0.03	0.01	0.02	0.04	0.02	0.02	0.05	0.16	0.3	0.3	0.38	0.48	0.34
K. pneumoniae	1,476	0.01	0.01	0.02	0.05	0.06	0.06	0.07	0.14	0.24	0.26	0.38	0.43	0.52	0.33	0.43	0.43
P. aeruginosa	5,159	0.74	0.74	0.7	0.64	0.53	0.61	0.68	0.81	0.82	0.88	0.83	0.96	0.95	1.03	1.11	1.09
S. marcescens	193	0.03	0.03	0.03	0.02	0.04	0.03	0.00	0.02	0.05	0.02	0.02	0.02	0.04	0.14	0.1	0.08

Figure 3 illustrates the number of unique patients (4,994) by pathogen from 2000 to 2015. Data shows that Psar was the most common CR pathogen for all years (2000-2015). However, other CROs emerged in waves as the second most common CR pathogen. Waves included CRAcat in 2010, followed by CR-Klpn in 2012 and CR-Ent in 2014.

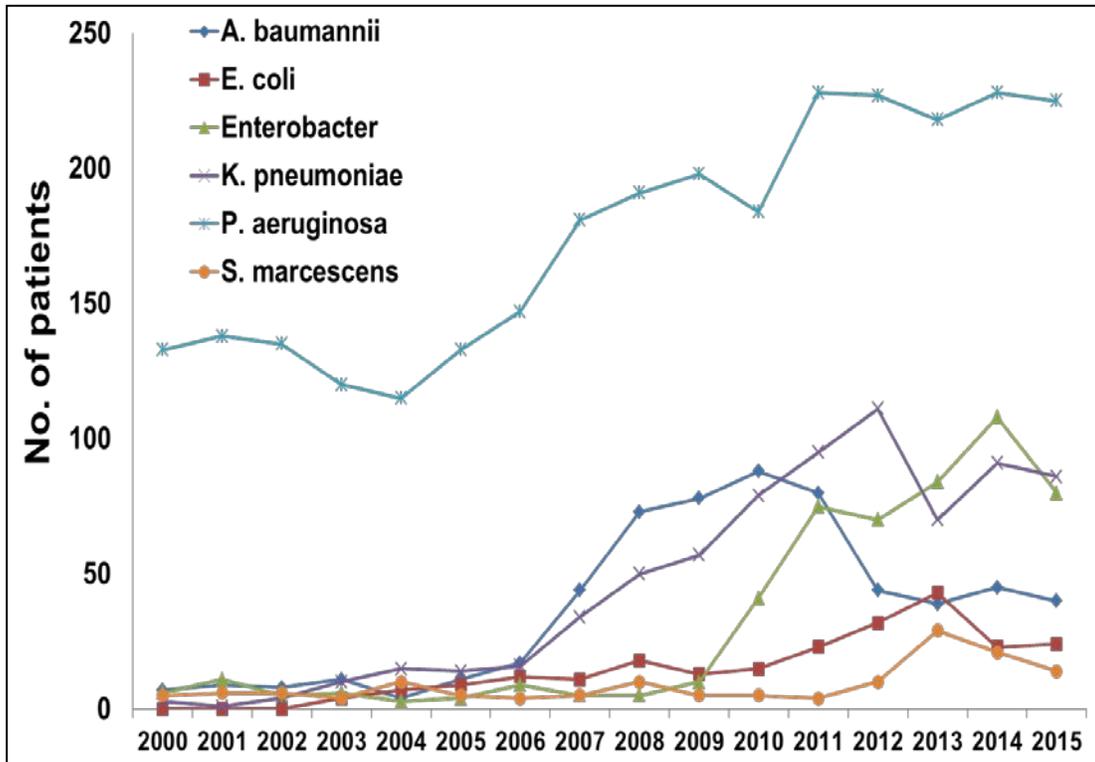


Figure 3. Unique patient CROs by pathogen at UPMC Presbyterian (2000-2015)

Rates of carbapenem resistance also changed significantly over time (Figure 4). Psar demonstrated the highest rates of baseline CR; however, from 2007 forward rates of CR among Acat were highest. Notably, CR emerged among previously susceptible pathogens, including Klpn, Ent, and Serm. In 2015, rates of CR exceeded 10% for every pathogen except Ecol.

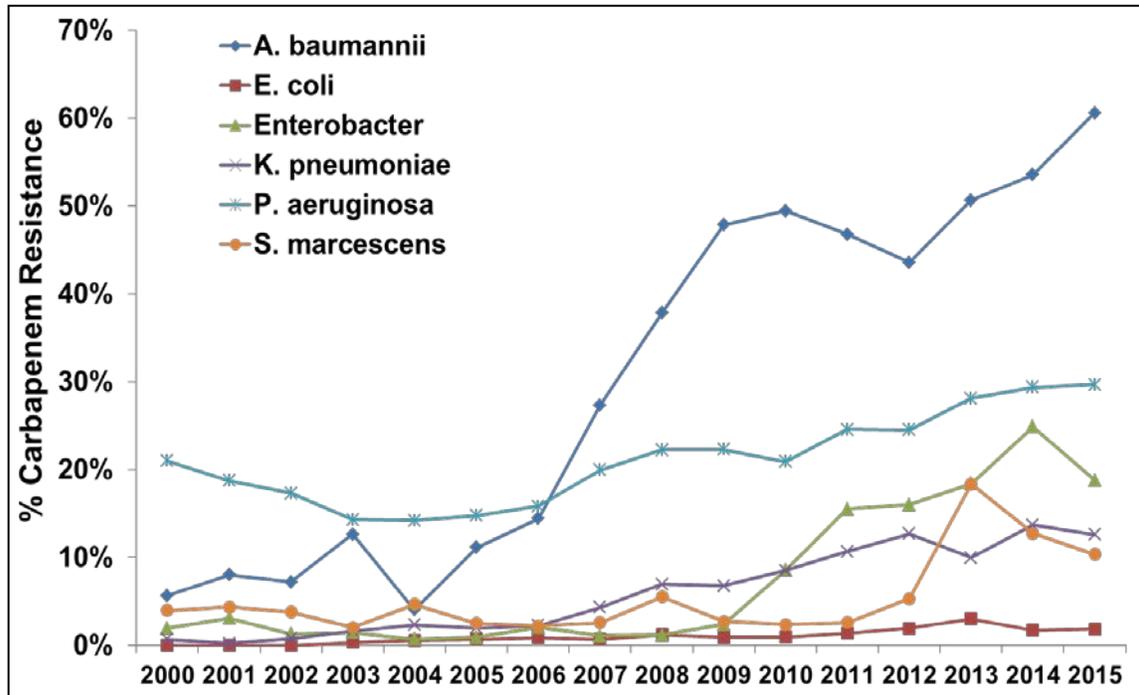


Figure 4. Carbapenem resistance by pathogen at UPMC Presbyterian (2000-2015)

Recurrence among patients with Psar was more common than any other pathogen. For these patients, recurrence was most commonly due to re-isolation of Psar after 90 days. On the other hand, 16% of patients who initially had CR-Klpn had a second CRO pathogen identified (Figure 5).

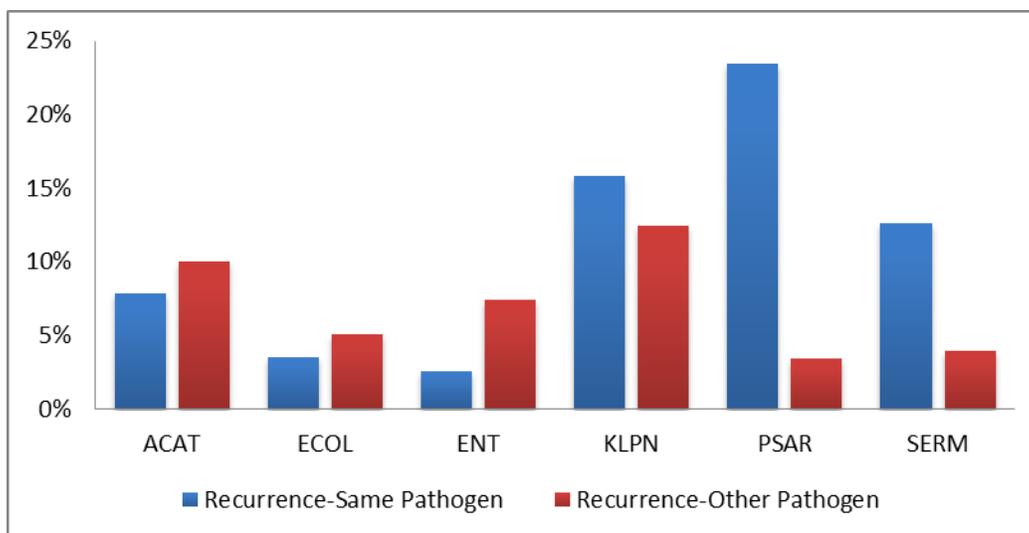


Figure 5. 90-day Recurrence rates by type of pathogen UPMC Presbyterian 200-2015

4.2 ANTIBIOTIC USAGE AT UPMC

Carbapenem DDD's increased significantly from 2000-2015 ($P < 0.001$) as shown in Figure 6. Increased rates of carbapenem DDDs paralleled patterns identified among the emergence of CROs. Indeed, cross-correlation analysis demonstrated a zero-lag time difference between the two ($R^2 = 0.90$, $P < 0.001$) (Figure 7). By pathogen, only Acat showed a time variance of -3 years suggesting the increases in carbapenem use were due, in part, to an increased frequency of CR-Acat isolation ($R^2 = 0.61$) (Table 5). Taken together, however, the cumulative data indicate that increased consumption of carbapenems and the emergence of CROs occurred simultaneously.

We further evaluated trends among DDDs for other antibiotic classes, but did not identify any associations with the emergence of CROs at our center (data not shown).

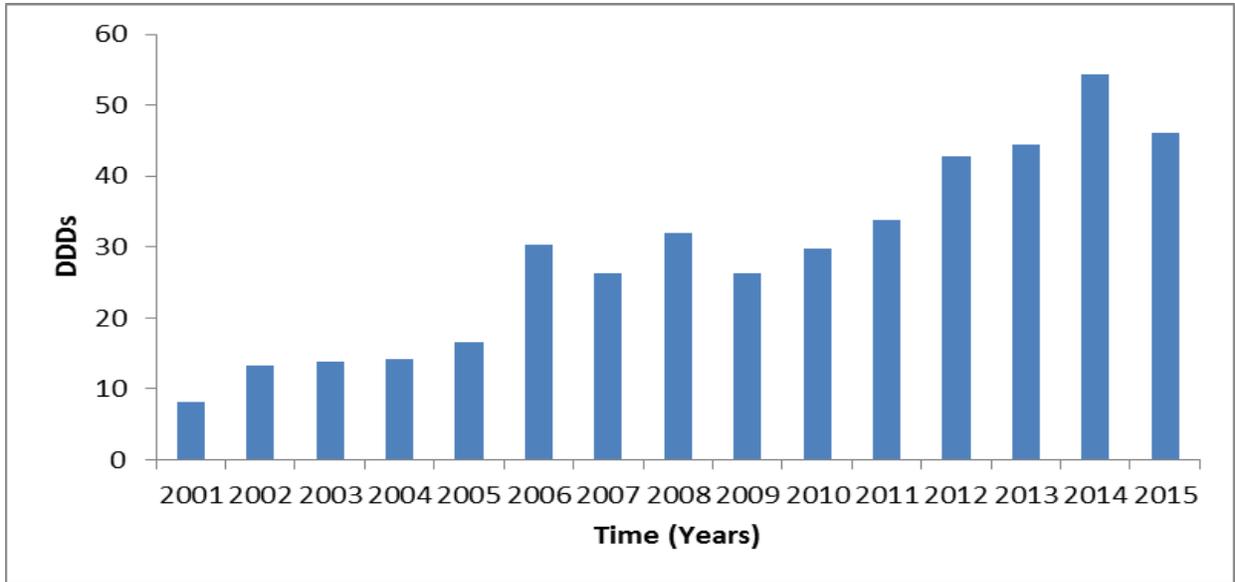


Figure 6. Carbapenem DDD use- UPMC Presbyterian 2000-2015

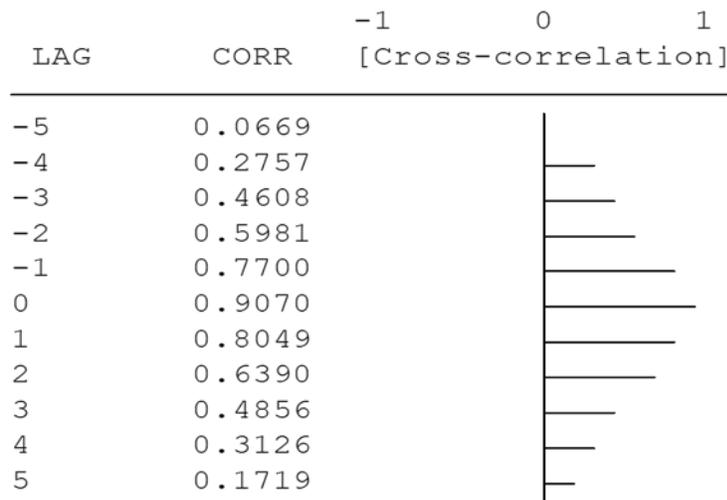


Figure 7. Cross correlation of DDD use with emergence of CROs UPMC Presbyterian 2000-2015

Table 5. Cross Correlation of DDDs by pathogen

	LAG	R-squared
ACAT	-3	0.61
ECOL	0	0.89
ENT	0	0.85
KLPN	0	0.88
PSAR	0	0.86
SERM	0	0.63
TOTAL	0	0.91

4.3 PATIENT CHARACTERISTICS

CROs were identified from 4,994 unique patients. Table 6 below describes the characteristics of these patients.

Table 6. Characteristics of patients with CROs at UPMC Presbyterian 2000-2015

Factor	All Patients (n=4,994)
Mean Age, years (std dev)	57.8 (± 15.9)
Male, N(%)	2,811 (56)
ICU at time of culture, N(%)	2,064 (41)
Solid Organ Transplant Recipient, N(%)	1,297 (26)

Twenty-six percent of patients were transplant recipients. . Transplant types included lung (51%), liver (23%), intestine (10%), kidney (8%), heart (5%), and other types (3%). Psar was more common among transplant recipients than non-transplant recipients ($P<0.001$). Conversely, CR-Acat was more common among non-transplants ($P<0.001$, Table 7).

Table 7. Pathogen Distribution by Transplant Status - UPMC Presbyterian 2000-2015

Pathogen	Transplant Patients (n=1,402)	Non-Transplant Patient (n=3,592)
ACAT	8.32%	13.01%
ECOL	2.54%	5.38%
ENT	5.55%	11.23%
KLPN	16.04%	14.66%
PSAR	64.15%	53.07%
SERM	3.39%	2.65%

4.4 MORTALITY

Overall 30- and 90-day mortality rates were 19% and 32%, respectively.

4.4.1 Predictors of Mortality

Age (OR=1.02, 95% CI:1.02-1.03, P<0.001) and ICU residence (OR=3.63, 95% CI:3.10-4.26, P<0.001) were independent predictors of 30d mortality illustrated in Table 8. On the other hand, receipt of a solid organ transplant was protective (P<0.001).

Table 8. Predictors of 30-day Mortality among Patients with CROs

Factor	Alive (n=4,022)	Dead (n=972)	P-value
Male, n (%)	2,237 (55.6)	574 (59.1)	0.09
Age > 65, n (%)	226 (5.6)	406 (41.8)	<0.0001
Residence in ICU, n (%)	1,410 (35.1)	654 (67.3)	<0.0001
Transplant recipient, n (%)	1,104 (27.4)	193 (19.9)	0.002

Specifically, patients who received intestinal and lung transplants had significantly different 30d mortality rates as compared to non-transplanted patients ($P < 0.001$ for both). All non-lung transplant patients also had a significantly different 30d mortality rate compared to non-transplants (Figure 8).

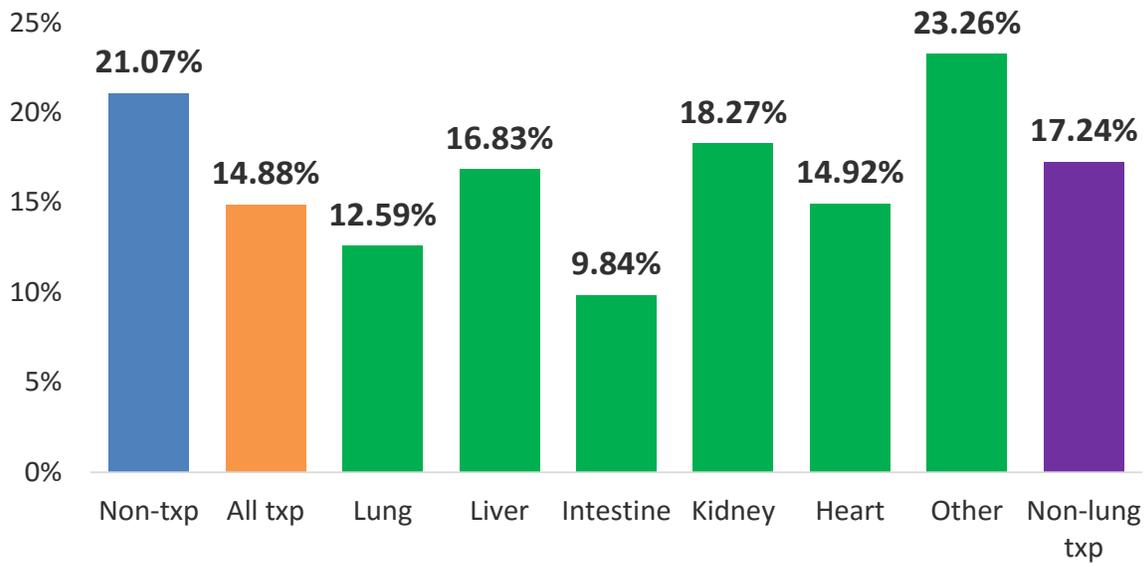


Figure 8. 30-day Mortality Rates by Transplant Type UPMC Presbyterian 2000-2015

By pathogen, mortality rates at 30d were higher for Acat compared to all organisms (28%, $P<0.001$), and lower for Psar compared to all organisms (17%, $P<0.001$, Figure 9). Rates ranged by culture site from 27% (blood) to 12% (urine, $P<0.001$, Figure 10).

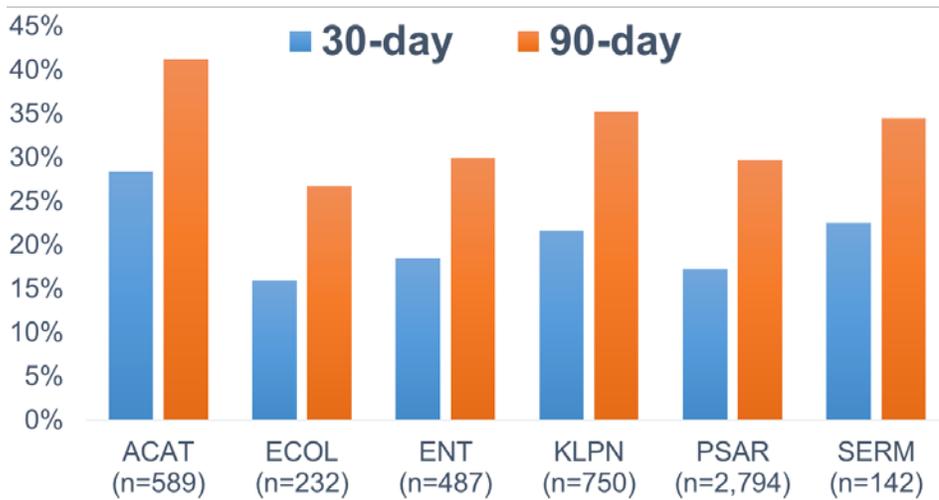


Figure 9. 30- and 90- day Mortality Rates by CR-Pathogen UPMC Presbyterian 2000-2015

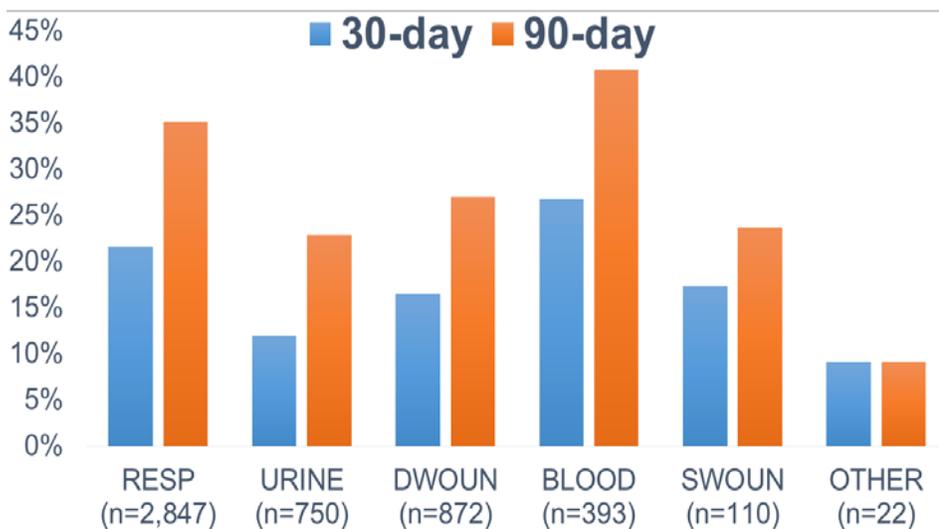


Figure 10. 30- and 90- day Mortality Rates by Culture Site UPMC Presbyterian 2000-2015

4.4.2 Survival Outcomes

In keeping with our univariate analysis, Acat was associated with lower rates of survival compared to all other pathogens at 30- and 90-days (Figures 11 and 12). Psar was associated with higher rates of survival compared to Acat ($P < .0001$) and Klpn ($P < .05$).

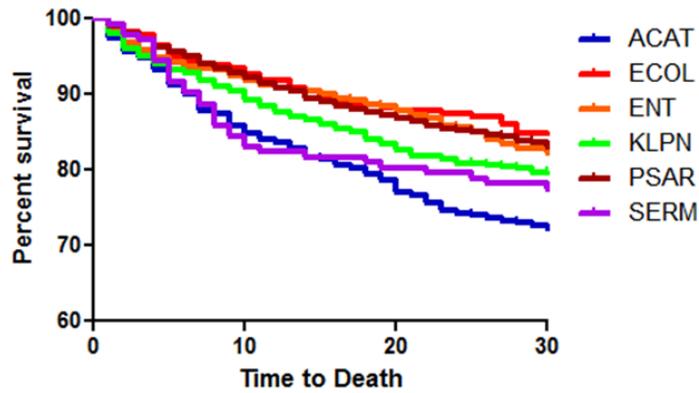


Figure 11. 30-day Survival Curves by CR-pathogen UPMC Presbyterian 2000-2015

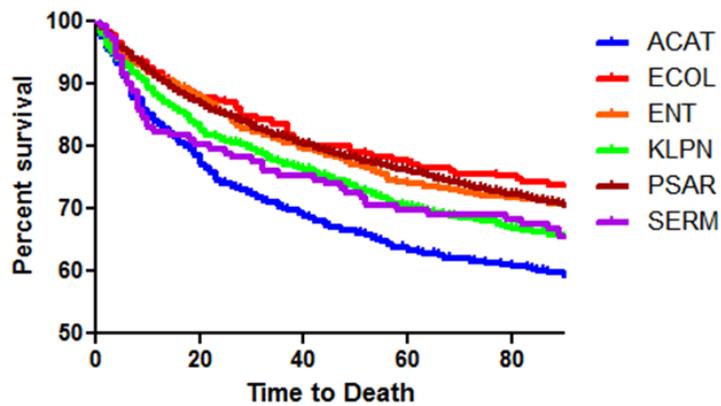


Figure 12. 90-day Survival Curves by CR-pathogen UPMC Presbyterian 2000-2015

Using logistic regression, we compared the risk of death for all variables (Table 9), and used coefficients from our model to derive 30-day mortality prediction equation (Figure 13).

Table 9. Independent predictors of 30-day Mortality UPMC Presbyterian 2000-2015 Mortality Prediction Model

Variable		β -coefficient	P-value
Intercept		-4.03	<0.001
Age		0.02	<0.001
Male		0.11	0.14
ICU		1.29	<0.001
SOT		-0.31	<0.01
Organism	ACAT	0.27	0.24
	ECOL	-0.28	0.32
	ENT	-0.24	0.33
	KLPN	0.07	0.75
	PSAR	-0.19	0.38
Culture	RESP	0.86	0.26
	URINE	0.51	0.50
	DWOUN	0.82	0.28
	BLOOD	1.20741	0.115
	SWOUN	1.002972	0.210

$$p = \frac{e^{a+B_1X_1+B_2X_2+..B_pX_p}}{1+e^{a+B_1X_1+B_2X_2+..B_pX_p}}$$

Figure 13. 30-day Mortality Prediction Equation

4.4.3 Mortality over Time

Annual mortality rates by pathogen were evaluated from 2007 to 2015, following the emergence of CR-Acat and CRE (Figure 14). Rates of 30-day mortality did not change significantly for Psar during this time period ($R^2=.15$, $P=NS$). On the other hand, the cumulative 30-day mortality rate of all other pathogens decreased from 28% in 2007 to 21% in 2015 ($R^2=0.73$, $P=.003$) (Figure 15).

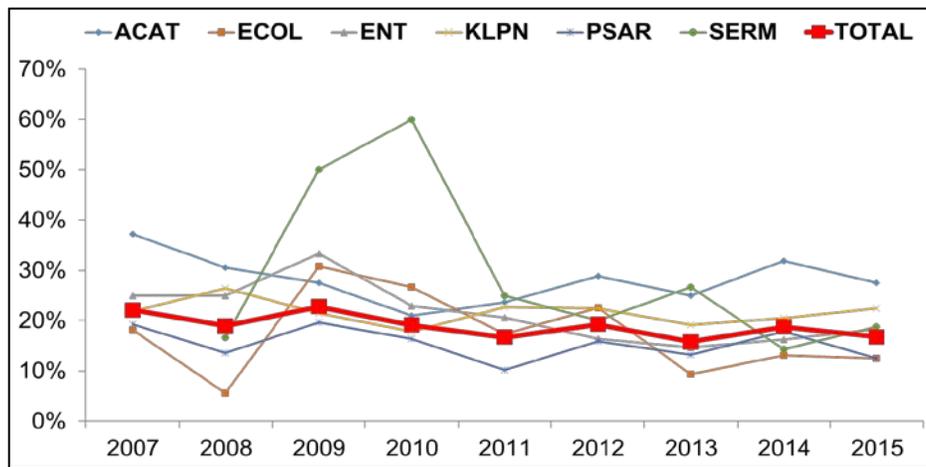


Figure 14. 30-day Mortality by Pathogen since 2007 UPMC Presbyterian 2000-2015

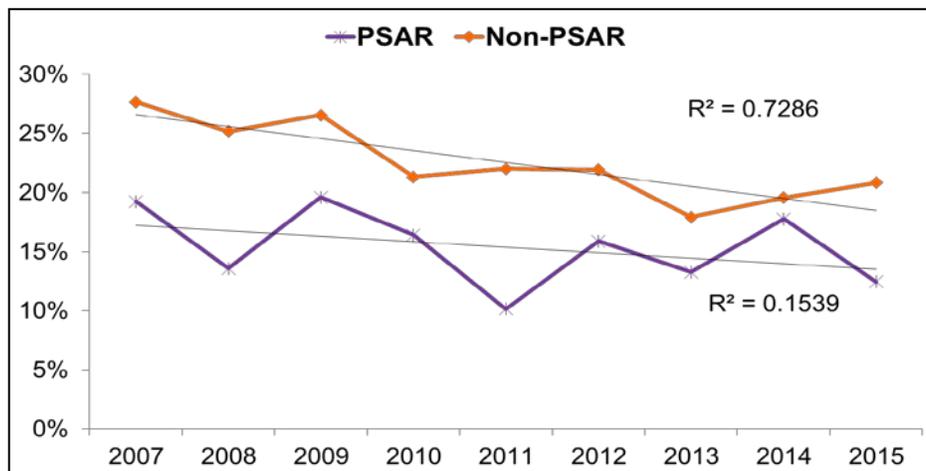


Figure 15. 30-day Mortality PSAR vs Non PSAR since 2007 UPMC Presbyterian 2000-2015

5.0 DISCUSSION

5.1 CARBAPENEM RESISTANCE EMERGES IN WAVES OVER TIME

We hypothesized that carbapenem resistance has emerged over time across many pathogens at our center, and our analyses supported these hypotheses. We found a statistically significant increase in CROs from 2000 to 2015. Psar consistently accounted for the largest number of unique patients with CROs. Furthermore, the emergence of other pathogens occurred at different time points over the surveillance period. Some of the emerging waves that were noted include Acat in 2010, Klpn in 2012, and Ent. in 2014.

Various theories could be considered for the cause of these emerging waves. One theory could be that once a pathogen specific outbreak is identified, targeted infection control investigations are launched to prevent the transmission of that pathogen. While infection preventionists are implementing strict surveillance in a specified location, the focus on one organism may distract staff from noticing an increase of another organism. This could be especially true if the secondary pathogen has been previously undetected.

Another theory that could account for the emergence of CROs is that diagnostics related to surveillance and identification have improved over time due to familiarity with these pathogens. Although we attempted to eliminate this potential confounder by retrospectively applying the 2015CLSI breakpoints, it is still a conceivable cause of the emerging waves of CROs that were identified. It is also possible that clinical standards in terms of surveillance could have changed

over the study duration. More specifically, if surveillance for these organisms increased over time we would expect to identify more CROs.

Consistent with the results of previous research, we hypothesized that antimicrobial usage would be associated with the emergence of carbapenem resistance at our center. DDDs of all classes of antibiotics were evaluated. We saw a significant increase in carbapenem use over the study duration. Conversely, a significant decrease in fluoroquinolone use was noted over time. This decrease in fluoroquinolone use is thought to be the result of antibiotic management which was implemented at UPMC in 2001.

When we compared the increase in carbapenem use to the increase of CROs, we did not see a causal relationship as expected. Prior research suggests that an increase in CROs would be expected after an increase in carbapenem use (Tun et al., 2016; Tuon et al., 2012). Instead, we concluded both the emergence of CROs and increased rates of carbapenem DDDs occurred simultaneously. Given that previous research does not agree with our findings, we were forced to consider alternative explanations. It is possible that 1-year time intervals may not have been sensitive enough to detect a subtle relationship.

One potential explanation for the emergence of CROs at our center is the level of care provided at our center. Given that we are a tertiary care center, there could be a higher number of patients coming into the center who are critically ill and could be housing these organisms prior to admission. One specific patient population to consider is those patients who are admitted from a nursing home or skilled nursing facility due to the acuity of care among this population. These patients are often colonized with MDROs, and upon admission to our center the organisms are provided with the opportunity to spread throughout our facility.

Another potential reason for the emergence of CROs at our center is geographic location. As the CDC suggest in their 2006 report, MDROs can be endemic. Western Pennsylvania sits within an endemic region of the United States for both CRE and CR Acat (CDC 2016).

5.2 CROs ARE ASSOCIATED WITH HIGH RATES OF MORTALITY

We hypothesized that patient outcomes vary by pathogen, severity of illness, and underlying diseases. We found that CROs are associated with high rates of mortality at our center. We further evaluated specific factors in order to better define which factors were potentially predictors of mortality.

Based on previous research, we anticipated that age >65 and residence in the ICU at time of culture isolation would both be associated with increased mortality (CDC, 2009a, 2009b; Chaisathaphol & Chayakulkeeree, 2014). We anticipated that age >65 could be a predictor of mortality as increased age alone is associated with higher mortality rates. Additionally, residence in the ICU is an expected predictor of mortality as patients in the ICU are critically ill and have increased comorbidities as well as invasive devices such as catheters or mechanical ventilation.

Among all pathogens, Acat was associated with the highest mortality rates. Acat is not a threat for healthy individuals; instead, Acat is known to affect those with chronic lung disease, diabetes, and weakened immune systems (Brotfain et al., 2016; Hsu et al., 2017). Multi-drug resistant Acat is considered to have an increased virulence that is associated with high rates of mortality (Stahl, Bergmann, Gottig, Ebersberger, & Averhoff, 2015; Thummeepak, Kongthai, Leungtongkam, & Sitthisak, 2016). Additionally, Acat was noted in several studies to be most commonly expressed in respiratory and blood infections which we know to have the highest mortality rates (Fujikura et al., 2016; Shields et al., 2012; Tsioutis et al., 2016).

Among culture sites, blood cultures were associated with the highest mortality rates. This was an expected finding. Although patients can be colonized with pathogens, this is not typically the case for blood culture sources. If the pathogen is identified in the blood, this is an infection and the patient will receive treatment. Other sources like urine and respiratory cultures are more likely to show the presence of a pathogen without the presence of symptoms or infection. These patients could be colonized, and a colonized patient who is asymptomatic would not receive treatment. Unlike the respiratory tract, blood is considered sterile. The presence of a microorganism in the blood typically elicits a profound immune response. This type of response to infection can lead to complications like sepsis. Furthermore, bloodstream infections are often associated multi-organ failure which contributes to increased mortality rates (CDC, 2016c). Since all positive blood cultures are true infections, we would expect CROs identified in the blood to be associated with higher mortality rates.

As found in previous studies, mortality rates did not vary between sex, which was also expected as previous studies do not suggest any correlation between sex and CRO mortality (Chaisathaphol & Chayakulkeeree, 2014; Shields et al., 2012; Tian et al., 2016). However, SOT was the only factor that resulted in an unexpected outcome. We found that SOT recipients had significantly lower rates of mortality ($P < .05$).

Solid-organ transplant recipients are a very unique population. This patient population is immunosuppressed in order to prevent rejection of the transplanted organ. Due to the increased risk of infection and mortality, we did not anticipate SOT to be a protective factor. Discovering that SOT patients at our center had a significantly lower mortality rate was rather surprising.

One theory to consider involves the Transplant and Infectious Diseases (TID) group at UPMC. These physicians are devoted to preventing infectious diseases in the SOT patient population, and accordingly undertakes active surveillance measures to identify infections early in

the disease course. They also aim to treat these patients as effectively as possible and often utilize prophylaxis. By treating SOT patients with prophylaxis at the time of transplant, this could potentially mitigate severe symptoms and help to improve this patient population's outcomes. Overall, the increased surveillance and treatment could potentially account for the lower mortality rates in this population.

Another potential reason for SOT being protective for mortality may be related to chronic colonization. One limitation to the data are that a positive culture does not delineate between infection and colonization. Patients experiencing an infection are symptomatic and require treatment. Colonized patients, conversely, are often asymptomatic and do not require treatment. Colonization typically occurs due to previous infection or increased exposure. SOT recipients frequent health care facilities and have an increased exposure to these organisms. Therefore, the likelihood of colonization could be higher in SOT recipients driving the outcomes to appear as protective.

CR-pathogen type among SOT recipients was another factor that we took into consideration. We found that CR-Psar was more common among SOT recipients. This is significant given that CR-Psar is associated with the lowest mortality rates. Therefore these lower rates could be driving the lower mortality rates among SOT recipients.

Additionally we were interested in which types of SOTs were developing CROs. Our center specializes in organ transplantation and has a very high volume of lung transplantations. Therefore, it was no surprise to find more than half of SOT recipients with CROs were lung transplant recipients. Although it was not an a priori hypothesis, we did expect that mortality rates would improve over time. One reason that we anticipated a decrease in mortality over time is due to new antibiotic availability. Various new antibiotics became available throughout the duration of this study. Some of the antibiotics that were FDA approved between 2001 and 2016 include but are

not limited ceftolozane-tazobactam (2014) and ceftazidime-avibactam (2015). Having new antibiotics available would help decrease mortality as patients are more likely to respond to a new antibiotic than an antibiotic that they may have developed resistance to from previous use.

Antibiotic management is another potential explanation for the decrease in mortality over time. At our center, antibiotic management was implemented in 2001. The purpose of antibiotic management is to oversee the prescription of antibiotics in order to prevent misuse and overuse of antibiotics. Additionally, this group has created algorithms over time that continues to allow refinement and improvement of treatment approaches over time. A recent study showed that antibiotic stewardship programs can decrease length of stay as well as 30-day readmission rates; overall they were shown to have a clinical benefit (Lee et al., 2016).

Another reason that mortality has improved over time could be due to improved diagnostics within the microbiology laboratory. Specifically, in 2015 the CLSI breakpoints were redefined. Fortunately, the antibiotic management program analyst designed and implemented a process to enable the application of these breakpoints retrospectively to ensure inclusion of all CR isolates in the same fashion. Given that the new breakpoints are more sensitive, there is a chance that a proportion of patients received inappropriate antibiotic therapy. In turn, the increased risk of inappropriate treatment in previous years could have led to increased mortality.

One of our primary aims was to develop a prediction model for patient mortality. Using coefficients from the logistic regression model, we were able to create a prediction model for patient mortality. A major benefit of having a prediction model would be related to treatment. Clinicians would be able to prospectively predict patient mortality. Having this type of information at baseline could be extremely beneficial for tracking a center's improvement in treating these drug resistant organisms. In theory, upon isolating a CRO one would simply enter the patient specific data for each factor within the model which includes the following: age, sex, hospital location,

SOT, pathogen type, and source type. Upon entering these data, the model would calculate a predicted mortality for that patient.

The primary strength of this study was its longitudinal nature and detailed patient-level data. Having such a large dataset provides a better understanding of the trends and epidemiology of CROs at our center. Additionally, standardization of the data over the time period was a great strength of this study. Some of the limitations included the lack of delineation between infection and colonization among CROs and the inability to classify severity of illness at the individual level.

In conclusion, this study found that CROs emerge in waves over time. We were able to define the epidemiology of these organisms at our center and gain an understanding of specific factors related to the emergence of CROs. We showed that there is no association between carbapenem DDDs and the emergence of CROs. Additionally, we were able to identify predictors of mortality, and utilize the data to create a prediction model which is the first of its kind. These findings have substantial public health significance as they provide a foundation for center-specific epidemiology of CROs.

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