Epidemiologic Risk Factors of Antimicrobial Resistance in Patients with Septic Shock Admitted to North American Critical Care Units: A Retrospective Study

By

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ABSTRACT

INTRODUCTION: Antibiotic resistance is a serious global threat resulting in a significant clinical and economic burden. The cost of caring for patients with resistant infections is high ($6,000-$30,000 USD 2008). The examination of resistance between different epidemiological groups is required to identify patient populations admitted to an intensive care unit (ICU) who may be more susceptible to life-threatening infections caused by resistant pathogens; it should also allow for preventative and treatment strategies aimed at reducing resistance and related complications, while improving outcomes, reducing ICU length of stay and corresponding health care costs.

PURPOSE: The specific aim of this retrospective study was to examine the frequency of resistant organisms among different epidemiological sub-groups of patients admitted to the ICU within the Cooperative Anti-microbial Therapy of Septic Shock (CATSS) Database with a diagnosis of septic shock and to determine independent predictors of the presence of antibiotic resistant organisms at the time of septic shock within this same population. The secondary specific aim was to describe the effect of the presence of antibiotic resistance on ICU and hospital mortality.

METHODS: We conducted a retrospective review of critically ill patients with septic shock within the CATSS Database between 1996 and 2012 (n=10,800). The presence of resistant organisms was assessed in relation to age, APACHE II, type and number of comorbidities, ICU admission source, and acquisition of infection (community vs nosocomial). Multivariable logistic regression analysis was

utilized to determine the independent predictors of presenting with antibiotic resistant organisms at the time of septic shock diagnosis. Individual multivariable logistic regression analysis models were used to determine independent predictors of ICU and hospital mortality after adjustment for the presence of resistant organisms.

RESULTS: Increasing age (OR 1.004 95% CI 1.001,1.007), liver failure (OR 1.27, 95% CI 1.028,1.463), ventilator dependence (OR 2.088, 95% CI 1.159,3.761), insulin dependent diabetes mellitus (OR 1.215, 95% CI 1.036,1.424), elective surgery (OR 1.332, 95% CI 1.166,1.521), emergent surgery (OR 1.244, 95% CI 1.045,1.482), neuromuscular disease (OR 1.540, 95% CI 1.153,2.057) and nosocomial acquired infection (OR 1.699 95% CI 1.517,1.904) were independent predictors of an increased odds of the presence of any antibiotic resistant organism at the time of septic shock diagnosis. The presence of leukemia (OR 0.797 95% CI 0.636, 0.998) and history of hypertension (OR 0.863, 95% CI 0.777, 0.958) were independent predictors of a reduced odds of the presence of any resistant organism. The presence of a resistant organism was significantly associated with an increased hospital but not ICU mortality in the univaraible model (OR 1.214 95% CI 1.118, 1.318) but did not show a significant association when adjusted for relevant covariates.

CONCLUSION: In this retrospective study of septic patients admitted to North American intensive care units, age, liver failure, ventilator dependence, insulin dependent diabetes mellitus, neuromuscular disease and nosocomial acquired infection were patient specific predictors of the presence of antibiotic resistance

organisms at the time of diagnosis of septic shock. Both elective and emergent surgery (vs medical diagnoses) was also associated with an increased odds for the presence of an antibiotic resistant organism. However, leukemia and history of hypertension were associated with a lower odds of the presence of antibiotic resistance. The presence of a resistant organism was associated with increased hospital but not ICU mortality in crude associations. We did not show significant association between resistance and mortality after adjustment for relevant confounders. Further research should focus efforts on these sub-populations for prevention of hospital acquired antibiotic resistance.

Preface

The data used for this project's analysis originates from an international research collaboration with the Cooperative Anti-microbial Therapy of Septic Shock (CATSS) Database working group, led by Dr. Anand Kumar from Sections of Critical Care Medicine and Infectious Diseases the University of Manitoba, Winnipeg, MB, Canada. Dr. Demetrios Kutsogiannis and Dr. Dean Karvellas are both collaborators at the University of Alberta. The literature review, data analysis and manuscript composition are original work by Tayne Hewer, under direct review and guidance from Dr. Demetrios Kutsogiannis. The subsequent research project, of which this thesis is part, will be submitted for ethics approval from the University of Alberta Research Ethics Board.

Acknowledgements

I would like to extend my deepest gratitude to the people who were instrumental for the completion of this research. First and foremost I would like to thank my supervisor and mentor, Dr. Demetrios Kutsogiannis. Dr. Kutsogiannis conveys a contagious excitement for research that can only be surpassed by his genuine delight in regards to teaching. His passion and ability for teaching truly sets a new standard for any endeavor in which one human being seeks to support the growth of another. Dr. Kutsogiannis' tireless support provided the perspective necessary to meet this standard, and his encouragement enabled me to surpass my own expectations. His gracious and selfless support, encouragements, expertise and leadership have helped me to grow as a professional, researcher, student, and as a person. Second, I owe a tremendous debt of gratitude to Pat Thompson. Every day, she serves as a reminder of the high standard of professionalism and ethical conduct for which I strive to achieve. She has been an outstanding mentor, and I am proud to call her a dear friend. She is a wealth of institutional knowledge and experience, and she far exceeded my expectations in availing me of those resources. Finally, I would like to thank my family. The unwavering support and enduring love they have provided for me over the years cannot be adequately summed up in words. The culmination of this effort marks a stepping stone in my academic and professional career. I can only hope that, when I take my next steps, I have access to professionals of the same caliber as Dr. Kutsogiannis and Pat Thompson. They truly transformed the task into an experience of personal and professional development, and continue to inspire me to do my best work.

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List of Abbreviations

APACHE II - The Acute Physiology, age and Chronic Health Evaluation Score

BSI – Blood Stream Infections

CATTS - Cooperative Antimicrobial Therapy of Septic Shock Database

CDC – Center for Disease, Prevention and Control

COPD – Chronic Obstructive Pulmonary Disease

ECDC – European Center for Disease and Control

ESCAPE/ESKAPE – Leading cause of nosocomial infections throughout the world including; Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species.

ICU – Intensive Care Unit

MDRO – Multidrug resistant Organisms

MRSA - Methicillin-resistant Staphylococcus aureus

SIRS – Systemic inflammatory response syndrome (SIRS)

SBP/DBP- Systolic and Diastolic Blood Pressure

WHO – World Health Organization

Glossary of Terms

Septic Shock: The database defined Septic shock according to the 1991 Society of Critical Care Medicine/American College of Chest Physicians consensus statement on sepsis definitions [16] and patients were included if they had documented or suspected infection, persistent hypotension requiring therapy with vasopressor therapy (a drop of systolic BP to <90 mmHg, and/or a drop in MAP to $\leqslant$ 60 mmHg that is unresponsive to fluid resuscitation or drop of 40 mmHg systolic in chronically hypertensive patients), and two of the following four elements: (1) a heart rate of > 90 beats/min; (2) a respiratory rate of > 20 breaths/min or Pco2 of <32 mm Hg; (3) a core temperature of <36°C; and (4) a WBC count of <4,000/μL, or > 10% immature (bands) forms.

Bacteremia: Primary bacteremia is only considered the source of sepsis in the absence of other possible septic sites.

Nosocomial Acquired Infection: Describes infections leading to septic shock that were acquired in acute care settings that were neither present nor incubating at the time of admission.

Resistant organisms: Defined as an isolate with non-susceptibility to at least one antibiotic agent. Bacteria and their resistance causing shock were defined based on blood cultures collected within 48 hours of presentation with septic shock

Comorbidities: Mutually exclusive data collection points. For example, if a patient had Insulin dependent diabetes, they were considered to have diabetes requiring medication and were captured *exclusively* under Insulin dependent diabetes. Appendix C outlines for details.

Documented infection: Culture positive in suspected infection/sepsis site. Can also be positive from biopsy or autopsy data. Also if clear cut on radiology (ie. necrosis of some kind, not just an infiltrate), or positive surgical identification (perforated bowel, ischemic bowel etc.)

Suspected infection: Culture negative in suspected septic site.

INTRODUCTION

Background

Antimicrobial resistance is a serious global threat resulting in a significant clinical and economic burden. Although antimicrobial resistance is a well-known phenomenon, the prevalence of resistant organisms continuous to increase significantly.

Clinical Burden

The United States Department of Health & Human Services Center for Disease Prevention and Control has defined Antibiotic / Antimicrobial resistance as the ability of microbes to resist the effects of drugs [24]. Antimicrobial resistance has been identified as a health care crisis and one of the most important problems for human health by the European Centre for Disease Prevention and Control (ECDC), the European Antimicrobial Resistance Surveillance Network (EARS-Net), the National Institute of Health and Allergy and Infectious Disease (NIH, NIAID), the World Health Organization (WHO) and the Canadian Government [21-24]. The WHO indicates that antibiotic resistance is one of the three most important public health threats of the twenty first century [23]. Each year in the USA, approximately two million people become infected with antibiotic resistant bacteria and at least 23,000 people die as a direct result of these infections [1, 21, 24]. In Canada, more than 18,000 hospitalized patients acquire infections that are resistant to antimicrobials each year and in 2014, the Canadian Government and Public Health Agency of Canada placed antimicrobial resistance as a national health care priority. Notably there has been a seven-fold increase in the incidence of Vancomycin-resistant Enterococci infections alone between 2007 and 2012 [34]. The Intensive Care over Nations Audit demonstrated that more than one-third of patients

develop an infection while being cared for in the ICU. Blood stream infections (BSI) are among the leading cause of infections resulting in ICU admission and septic shock has been established as the leading cause of death in ICU's with approximately 40,000 deaths/year in the US and 20,000 deaths/year in Canada [36-38,41]. Mortality is three-fold higher in those with septic shock versus those not affected [8,9,13]. Antibiotic resistance is an established threat to public health and resulting in the compromised treatment of infected patients, in particular the treatment of the critically ill [21,48, 59,65].

Antimicrobial resistance has been attributed to the overuse and misuse of antimicrobial medications and a lack of new drug developments and is associated with unfavorable clinical outcomes including delay in appropriate antibiotic treatment and effectiveness, increased antibiotic toxicity, improper dosing, increased mortality rates, increased surgical requirements, and longer hospital lengths of stay [2, 7,10, 14, 15, 22, 28, 40, 45, 47-50].

Economic Burden

There is a significant economic burden as a result of antibiotic resistant organisms [3, 4, 47, 59]. The cost of caring for patients with resistant infections is high ($6,000-$30,000 USD 2008) and the total annual cost of antimicrobial resistance was estimated to be approximately US $ 30 billion/year in 1995 [1, 2] Bloodstream infections alone in ICU's are associated with and 2-7 day increased ICU length of stay and 2-3 week increased hospital length of stay with attributable excess costs of $25,000-40,000 [37, 38, 59].

Mechanisms of Antibiotic Resistance

Antibiotic resistance continues to advance in the clinical setting and far out-paces the strategies to combat resistance. Understanding the mechanisms of the development of resistance in an organism is important and complex, especially the emerging resistance that is currently seen in clinical settings. A thorough understanding of the mechanisms of antimicrobial resistance and the populations at risk for developing resistance is fundamental in preventing its escalation. There are two main genetic mechanisms well known to the development of acquired resistance, mutations or genetic exchange [25, 28-30, 33]. Mutations result in resistance by changing or affecting the action of the antibiotic compound. This can be achieved by altering the target of the antibiotic, decreasing the uptake of the antibiotic, activation of mechanisms to remove the antibiotic, or changes in metabolic and regulatory pathways rendering antibiotics ineffective. Genetic exchange resulting in antibiotic resistance can be achieved by bacteria through transformation, transduction or conjugation. The most common type of genetic exchange seen in hospital or clinical setting is that of cell to cell contact (conjugation), providing an issue for neighboring patients to those affected with a resistant organism as a result of patient-patient transmission or and staff cross-contamination [24,33]. The main mechanisms of antibiotic resistance are outlined in Figure 1.

Risk Factors of Antibiotic Resistance

Several risk factors have been identified in the development of resistant infections including: increasing age, underlying illness, requirement of invasive devices or procedures, exposure to ICU or hospital settings, prior hospitalization, and antibiotic use [13, 30-32, 40, 45].

Age

Patients of increasing age, specifically the elderly, are at the greatest risk for death and complications from infections [51, 52, 54-56]. This is thought to be the result of chronic underlying diseases, delays in diagnosis and therapy, poor tolerance or complications from procedures, delayed or poor response to antibiotics, and greater risk and incidence of nosocomial infections [51-53]. A retrospective study of Methicillin-resistant Staphylococcus aureus (MRSA) infections by Garcia et al [56] outlined the importance of patient age during physicians consideration of antibiotic selection, demonstrating that the number of antibiotic resistant organisms were higher in the older population, specifically when treated with antibiotics, such as fluoroquinolones, that target DNA synthesis. Given the known clinical implications of increased age on complications, risk of infection, and risk of morbidity and mortality, this epidemiological factor is of increased importance when considering the impact of resistant organisms.

Underlying Illness, Illness Severity

The presence of underlying illness and the severity of illness are well studied factors associated with increased complications, morbidity and mortality among patients who are critically ill. Patients with antibiotic resistant infections are likely to have more severe underlying disease, and the mere presence of comorbid conditions, such as diabetes and vascular disease, are among many factors that contribute to the increased risk of infection with antibiotic-resistant bacteria (58, 60, 62-65). A five year-retrospective cohort study of surgical ICU patients with bacteremia conducted by Pittet et al, concluded that the assessment of pre-existing co-morbidities at ICU admission significantly improved the prediction of mortality compared to APACHE II score alone in

patients with from bacteremia [60,62]. Illness severity is an important confounder when assessing the effect of resistant organisms on mortality and clinical outcome as illness severity has been shown to impact both antibiotic resistance and mortality independently [62].

AIDS

Patients with HIV/AIDS represent a population at increased risk of developing nosocomial resistant infections. This is attributed to their frequent contact with the health care system and immunocompromised system. Several studies have showed that blood stream infections are the most common hospital acquired infection in HIV positive patients. Additionally HIV positive patients represent a population at increased antibiotic resistance risk due to neutropenia [30].

Ventilator Dependence and Use of Invasive Devices or Surgical intervention

Patients requiring mechanical ventilation represent a patient population at increased risk for infection [11]. In a retrospective matched cohort study of patients with Acinetobacter bacteremia there was a 5 day excess length of mechanical ventilator dependence and ICU stay compared with critically ill patients without Acinetobacter infection [6].

Patients infected with antibiotic resistant organisms often require surgical intervention to control the infection, leading to an increased risk of complications and morbidity known to be associated with surgical procedures [3-4, 15]. A retrospective cohort study of 689 adults who underwent elective surgical procedures and developed postoperative infections demonstrated that 49% of patients developed an infection that was resistant to antibiotics. However, the development of antibiotic resistance was not significantly associated with antibiotic prophylaxis [57]. While several studies have

failed to demonstrate a significant association between the use of surgical prophylactic antibiotic and post-operative development of antibiotic resistant organisms. This relationship required further investigation.

Antibiotic Use

In the hospital settings, antibiotic use is highest in ICU patients due to their inherent increased complexity and infection rates. As a result, rates of developing and persisting resistance that are not adequately treated are also high in this population, leading to a 70% increased likelihood of death [14]. Of the causes of antibiotic resistance, antibiotic misuse or overuse is of the most studied. Inappropriate or unnecessary use of antibiotics accounts for 30-50% of the total burden of antibiotic associated resistance [10,15, 58,]. Johnson et al conducted a retrospective study of hospital patients with severe sepsis and septic shock caused by gram negative microorganisms, and demonstrated that prior antibiotic exposure was associated with a reduced susceptibility to cefexime, piperacillin–tazobactam, carbapenems, ciprofloxacin, and gentamicin, and that these patients more frequently received inappropriate empirical antibiotic therapy and had a higher hospital mortality [14]. Further, in a retrospective cohort study of 510 patients with Enterobacteriacea bacteremia, Brunham et al found that the presence of multidrug resistance did not appear to influence patients' outcomes when the initial therapy was appropriate for the causative pathogen [18]. Similarly, Zilberberg et al concluded that inappropriate antibiotic therapy used as initial treatment of gram-negative bacteremia and severe sepsis/septic shock was the reason for multidrug resistant organisms [19].

Hospital Acquired infections (HAI) – Hospital Exposure, Length of Stay

A number of studies have described prior or extended hospitalization as a risk associated with increased risk of developing resistant organisms. Hospital acquired infections are the most common complication seen in hospitalized patients. Hospital acquired infections increase morbidity, mortality, costs and length of stay even after adjustment for underlying illness. In 2003, HAI affected 2 million patients annually in the US and accounted for 90,000 deaths per year making nosocomial infections the fifth leading cause of death in acute care hospitals. It has been estimated that 25% percent of hospital acquired infections occur in the intensive care units resulting in increased length of stay and health care costs [27,30]. However, the higher rate of resistance in hospitals may be attributed the fact that the number of patient's receiving antibiotics or adhering to antibiotic consumption in hospital are higher than in the community [26].

A study of 346 patients (1997-2000) with clinically significant staphylococcus aeaurus bacteremia showed that among survivors, methicillin resistance was associated with significant increases in the median length of hospital stay after acquisition of infection (9 vs 7 days for patients with MSSA bacteremia) represented a 1.3 fold increase in hospital length of stay [5].

Types of Resistant Organisms

The Centers for Disease Control and Prevention (CDC) has categorized specific bacteria as presenting both a clinical and economic burden on the health care system; ESKAPE or ESCAPE represents this comprehensive classification of resistant pathogens that account for more than 80% of the infectious episodes in the ICU these include: E faecium, S aureus, K pneumonia, A baumannii, P aeruginosa, and Enterobacter spp [21, 24, 33].

Clostridium difficile has been recently added to this list. In Canada, Clostridium difficule, Carpeneum resistant organisms such as eterboactericoace, MRSA and streptococcus pneumonia are the leading organisms causing hospital acquired infection under surveillance [21, 24, 32]. In the US, the rate of resistant Clostridium difficule infections continues to grow [46]. In a multicenter retrospective study of Canadian Hospitals by Ramirez et al 25% of prevalent Staphylococcus aureus bacteremias in the ICU were methicillin-resistant, and 10% of Pseudomonas aeruginosa bacteremias were resistant to meropenem [39].

Resistance and Mortality

The presence of resistant organisms has been linked to a decreased effectiveness of antibiotic therapy, improper dosing of antibiotics, delay in effective treatment, increased requirement for surgery and increased morbidity and mortality [15, 19, 20, 49, 50]. Mortality rates are higher for patients who receive inappropriate or delayed antibiotic treatment [15]. For these reasons it important to determine the association between the presence of resistant organisms and mortality independent of underlying illness severity and associated complications.

Current initiatives

There have been multiple attempts to combat resistant organisms including, the development of new drugs, infection control and antibiotic stewardship programs. Among these attempts, there has been interest in identifying patient populations considered to be at risk for antibiotic resistant organisms. Various scoring systems have been explored with the aim to develop efficient methods to diagnose resistance. Unfortunately the value of these scoring systems is limited [10]. Despite advantages, there has not yet been a

single prediction score for treatment of ESKAPE pathogens that has been widely used and accepted. Most clinicians use certain risk profiles (complex ICU stay, recent prior hospitalizations, prior long term care or recent antibiotic exposure) to assess the need for broad spectrum antibiotics, leading to issues of risk scores being non-specific or broad [7,11,27, 33-35,61]. Moreover, methods currently used for early detection of antibiotic resistance tend to require additional resources, and take more than a day to yield results. Even rapid methods that allow for prompt and targeted therapy, require specific training and personal and come at an additional cost (i.e. multiplex immunocapture-coupled PCR) [12].

Limitations in Current Research

Major methodological differences between studies contribute to the difficulty in comparing prevalence of resistant organisms and its treatment. In 2011, the ECDC implemented a protocol for point prevalent studies of hospital acquired infections in acute care hospitals. While steps to rectify these differences have been made, there still exists a large inconsistency among studies in methodology including controlling for underlying comorbidities and illness severity [9, 14, 21, 23, 36, 42].

The ECDC are currently conducting a survey of European Intensive Care physicians with respect to experience with infections in an attempt to describe antibiotic prescribing practices in ICUs.

Call for Future Research

<u>Antibiotic Resistance</u>

While the phenomenon of antibiotic resistant organisms is among the leading global health initiatives, the magnitude of its impact and current strategies to combat it remain

largely unknown and generally ineffective. Moreover, the majority of current initiatives are costly, time consuming and require large resources. Global antibiotic stewardship initiatives have been developed with aim to target factors contributing to the development and transmission of resistant organisms by focusing on appropriate antibiotic prescribing, and early detection of resistant organisms. This thesis manuscript falls under the initiative for developing tools to characterize high risk populations for antibiotic resistance for the purposes of early detection. Early detection and subsequent drug monitoring may help optimize drug administration and support a patient-specific approach [7, 22, 35, 44]. Accreditation Canada has made antimicrobial stewardship a required organizational practice for all acute care hospitals [34].

Septic Shock Patients

As a result of the increasing age and complexity of critically ill patient populations, an increased prevalence of antibiotic resistance, and the high morbidity and mortality associated with blood stream infections and septic shock, ICU patients represent an important population of study.

Risk Factor Stratification

In order for prediction scores or risk stratification to be successful, they should be simple, and consist of parameters that can easily be deduced at the patient's bedside during an initial clinical encounter [10, 42, 44]. The data obtained from this observational study on patient specific characteristics associated with the presence of antibiotic resistance at the time of diagnosis of septic shock may assist in informing the development of bedside strategies or prediction tools to identify patients at risk for the purposes of optimizing antibiotic prescription.

Cost Effectiveness

Since risk stratification can be achieved with relatively little intervention or technology, it could be a simple and cost effective tool used to identify and rationally prescribe antibiotics to critically ill patients at risk of developing resistant infections.

Guiding Local Practice

While there are several international surveillance systems in place for antibiotics (i.e. EARSS) the challenge remains on how to effectively translate this knowledge to inform local practice and physician prescribing of empirical therapy.

Consideration of Illness Severity and Comorbidities

Heterogeneity of patient populations within the critical care setting needs to be further considered when examining the frequency of antibiotic resistant organisms and guidelines need to incorporate the severity of patient illness to provide a personalized patient approach [7, 42, 44].

The examination of resistance between different epidemiological groups is required to identify patient populations admitted to an intensive care unit (ICU) who may be more susceptible to life-threatening infections caused by resistant pathogens; it should also allow for targeted treatment strategies aimed at reducing resistance and related complications, while improving long term outcomes, reducing ICU length of stay and corresponding health care costs.

PURPOSE

Primary Specific Aim

The specific aim of this retrospective study was to examine the frequency of resistant organisms among different epidemiological sub-groups of patients admitted to the ICU within the Cooperative Anti-microbial Therapy of Septic Shock (CATSS) Database with a diagnosis of septic shock; and to determine independent predictors of the presence of antibiotic resistant organisms at the time of septic shock in this same population.

Secondary Specific Aim

The secondary specific aim was to describe the effect of the presence of antibiotic resistance on ICU and hospital mortality.

METHODS

Study Design: Patient Population and Study Setting

We conducted a retrospective review of critically ill patients with septic shock within the Cooperative Anti-microbial Therapy of Septic Shock (CATSS) Database between 1996 and 2012. The patient population included all patients admitted to a participating academic or community hospital ICU with a final diagnosis of septic shock (including transfers). Patient charts were identified for the database using pre-existing ICU databases/registries or billing records.

Sample Size

This retrospective study was conducted on a convenience sample of patients who went into septic shock, captured in the existing CATTS database. Data were extracted for all patients (N=10,800). A sample size calculation to describe the magnitude of our convenience sample is outlined in Appendix E.

Operational Definitions

The database defined Septic shock according to the 1991 Society of Critical Care Medicine/American College of Chest Physicians consensus statement on sepsis definitions and patients were included if they had documented or suspected infection, persistent hypotension requiring therapy with vasopressors *(a drop of systolic BP to <90 mmHg, and/or a drop in MAP to ≤ 60 mmHg that is unresponsive to fluid resuscitation or drop of 40 mmHg systolic in chronically hypertensive patients),* and two of the following four elements: (1) a heart rate of > 90 beats/min; (2) a respiratory rate of > 20 breaths/min or Pco2 of <32 mm Hg; (3) a core temperature of <36°C; and (4) a WBC count of <4,000/μL, or > 10% immature (bands) forms [16].

Resistant organism was defined as an isolate with non-susceptibility to at least one antibiotic agent. All cultures collected in the database were from the time of presentation with septic shock. A quantitative culture result was available when multiple organisms were isolated from the same site (heavy vs moderate vs light 4+ 3+). Predetermined rules were used to define documented and suspected infections and to assign significance to clinical isolates as previously described. Pathogen and their resistances causing shock were defined based on blood cultures that were collected within 48 hours of presentation with septic shock [15, 17].

Nosocomial infection-related septic shock was defined as septic shock caused by any infection developing > 48 hours after hospital admission [17].

Documented infections were those in which a plausible microbial pathogen was identified from the clinical infection site or blood in the context of a compatible clinical syndrome or in which infection was supported by a definitive radiologic, surgical, or

pathologic diagnosis (autopsy or biopsy). All other infections were considered to be suspected [17].

Data Integrity, confidentiality, cleaning and variable Selection

Data from the database was collected by trained research coordinators at each site. A minimum of 10% of the charts at each site were required to be randomly audited by the principal investigator or surrogate to ensure appropriate data extraction.

All data transferred and used for local data analysis for this study was de-identified prior to receipt. Data was analyzed in aggregate fashion. No local cases were used in this analysis. Ethics approval will be submitted for future contribution of local cases for the CATSS database.

The variables in the dataset were reviewed at great detail with the local study investigator, Dr. Demetrios Kutsogiannis and an additional data dictionary created to mirror/supplement the documents provided by the lead site. The full dataset was provided in an excel document and data was cleaned by removing all existing formulas and pre-calculated statistics. A detailed description of this data cleaning processes and data dictionary has been provided in Appendix A.

Variables in the data base were initially assessed for topic relevance and descriptive epidemiological sub group variables of the population were identified. Further, variables thought to be of clinical relevance to the development of resistant organisms either by review of the literature or clinical judgement were included in the initial subset.

<u>Outcome Variables</u>

The primary outcome was the presence of any resistant organism at the time of septic shock diagnosis. The CATSS database captured up to three resistant organisms for

each patient. The outcome variable, presence of any resistant organism, was transformed by coding yes, if the patient had ≥ 1 organism that was resistant to antimicrobial therapy. This variable was closely examined for each patient to ensure successful re-coding. Disease severity was an important confounder controlled for in both multivariable analysis and quantified by the APACHE II score. This is a well-accepted validated scoring system for predicting ICU mortality.

The secondary outcomes were ICU and hospital mortality, as measured by death at any point during ICU and hospital stay respectively. The presence of resistant organisms was assessed in relation to age, illness severity as measured by APACHE II, type and number of comorbidities (Appendix D), admission source (emergency room, medical or surgical ward, other hospital ICU), acquisition of infection (community vs nosocomial) and the use and number of antibiotics. Similarly, both ICU and hospital mortality were assessed in relation to age, illness severity as measured by APACHE II, type and number of comorbidities, admission source (emergency room, medical or surgical ward, other hospital ICU), acquisition of infection (community vs nosocomial), the presence of resistant organisms and length of ICU and hospital stay.

Length of Stay Variables

The natural logarithms of ICU and hospital length of stay, as potential confounders, were also included for the purpose of the in the mortality outcome analysis. However, they were not included in the multivariable logistic regression determining independent predictors of the presence of resistance. This was because the present data relate to the pathogens and their resistance at presentation with septic shock, so the length of stay would not affect the point prevalence of resistance organisms but instead be related in

that length of stay may be increased for patients with septic shock due to a resistant pathogen.

Multivariable Analysis

Multivariable logistic regression analysis was utilized to determine the independent predictors of presenting with antibiotic resistant organisms among all ICU patients with prevalent septic shock. All variables with significance of $p \leq 0.20$ were included in the multivariable regression models.

STATISTICAL ANALYSIS

Univariate analysis was performed using Chi Square test for independence or Fischer's exact for categorical variables. Simple logistic regression was used for continuous variables. Continuous variables were reported as means with standard deviations. Categorical variables were expressed as frequencies. A p value of ≤ 0.05 was considered significant. Factors associated with resistance in a univariate analysis ($p \leq 0.20$) were then entered into a multivariate logistic regression analysis to determine odds ratio. Variables were reviewed with Dr. Kutsogiannis and biologically plausible factors were also included if they did not reach this level of significance (Ventilator dependence and APACHE II). The Kolmogorov-Smirnov Test was used to determine the distribution pattern of length of stay variables, both were transformed using their natural logarithms (Appendix A). All variables entered into the model were reviewed and assessed for collinearity and separate multivariable models were created independently with ln ICU and ln hospital length of stay. All analysis was done using IBM SPSS Statistics 19.

RESULTS

Demographic and Descriptive data

The study included 10,800 patients who went into septic shock bloodstream infections in the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database. The mean age was 62.8 ± 16.1 years and 55.9% were males. The mean acute physiology and chronic health evaluation (APACHE) II score was 25.2 ± 8.1. Over eighty percent of patients had at least one comorbidity (9650). Trauma accounted for 38% of patients admitted to the ICU, followed by 28% patients admitted with a medical cause. Pneumonia was the leading source of infection (39.1%) and 28.9 % patients were admitted with a gastrointestinal source of infection, representing two of the most common sources of infection. Out of 10800 patients, 86.2 % (*n*=9,312) had a documented infection verse 13.8% with a suspected infection (*n*=1,488). Overall 6846 patients (63.4%) had community acquired infections and 3954 patients (36.6%) had nosocomial acquired infections. Escherichia coli bacteria species was found in 14.9% of the population and 6.7% of the population developed Escherichia coli bacteria as the primary resistant organism. Staphylococcus aureus was found as the primary organism of infection in 11.8% of the population and 3.5% of the population developed Staphylococcus aureus as the primary resistant organism (n=378). Baseline characteristics are further outlined in Table 1.

Hospital Outcome Descriptive Data

The mean ICU and hospital length of stay was 10.49 ± 12.9 days and 27.37 ± 35.7 days, respectively. Of 10,800 patients with septic shock 4305 (39.9%) died in the ICU and

5337 (49.4%) died in hospital. Of the deceased population, a combined 31.5% presented with at least one resistant organism at the time of septic shock diagnosis.

Characteristics and Predictors of Patients with Resistant Organisms

Univariable analysis demonstrated that increasing age ($p = 0.032$), illness severity as measured by APACHE II ($p = 0.032$), elective and emergent surgery ($p \leq 0.001$), ventilator dependence ($p = 0.011$) and the presence of at least one comorbidity ($p \leq 0.001$) were significantly associated with the presence of a resistant organism at the time of presentation of septic shock. Overall, 2980 patients (92.0%) presenting with a resistant organism at the time of septic shock had at least one comorbidity. Of patients with a hospital acquired infection, 38.6% had at least one resistant organism. In comparison, 25.1% of those with community acquired infections were resistant to at least one antibiotic therapy.

After adjustment for covariates, increasing age (OR 1.004, 95% CI 1.001,1.007), liver failure (OR 1.27, 95% CI 1.028,1.0463), ventilator dependence (OR 2.088, 95% CI 1.159,3.761), insulin dependent diabetes mellitus (OR 1.215, 95% CI 1.036,1.424), elective surgery (OR 1.332, 95% CI 1.166,1.521), emergent surgery (OR 1.244, 95% CI 1.045,1.482), neuromuscular disease (OR 1.153, 95% CI 1.153,2.057) and nosocomial acquired infection (OR 1.699 95% CI 1.517,1.904) were independent predictors of an increased odds of the presence of a resistant organism at the time of septic shock diagnosis. The presence of leukemia (OR 0.797 95% CI 0.636, 0.998) and a history of

hypertension (OR 0.863 95% CI 0.777, 0.958) were independent predictors of a reduced odds of presenting with any resistant organism.

Survival Outcomes

Univariable analysis demonstrated that increasing age ($p \leq 0.001$), illness severity as measured by APACHE II ($p \leq 0.001$), nosocomial acquired infection ($p \leq 0.001$), lymphoma ($p \leq 0.001$), leukemia ($p \leq 0.001$), metastatic cancer ($p \leq 0.001$), immunosuppression ($p \leq 0.001$), neutropenia ($p \leq 0.001$), liver failure ($p \leq 0.001$) heart failure symptoms (New York Class IV) ($p \leq 0.001$), chronic heart failure (*ICU* $p=0.043$, *hosp* $p \leq 0.001$), hypertension ($p \leq 0.001$), medication requiring diabetes mellitus ($p=0.003$) IV drug use ($p \leq 0.001$) neuromuscular disease (($p \leq 0.001$) admission from emergency room, medical ward, and increasing ICU and Hospital length of stay ($p \leq 0.001$) were significantly associated with both ICU and hospital mortality. Intermittent hemodialysis ($p=0.03$), severe COPD ($p=0.001$), emergent surgery ($p=0.009$*),* and the presence of a resistant organism ($p \leq 0.001$) was significantly associated with hospital but not ICU mortality in the univariable analysis.

Hospital Mortality

After adjustments for covariates: age, (OR 1.026 95% CI 1.123, 1.030) APACHE II (OR 1.099 95% CI 1.091, 1.107) nosocomial acquired infection (OR 2.040 95% CI 1.790, 2.325), AIDS (OR 2.318 95% CI 1.650, 3.257), liver failure (OR 3.359 95% CI 2.697, 4.184), and NY Class IV heart failure (OR 1.444 95% CI 1.035, 2.015) were independent predictors of an increased odds of hospital mortality. Additionally, Lymphoma (OR 1.987 95% CI 1.469, 2.687), metastatic cancer (OR 1.363 95 % CI 1.149, 1.617), chronic dialysis (OR 1.395 95% CI 1.085, 1.793), emergent surgery (OR 1.339 95% CI 1.087,

1.649) and admission from a medical ward (OR 1.439 95% CI 1.239, 1.672) were independent predictors of an increased odds of hospital mortality but not ICU mortality when adjusted for hospital length of stay. Patient history of hypertension (OR 0.816 95% CI 0.723, 0.921), admission to ICU from an emergency room (same hospital; OR 0.729 95% CI 0.622, 0.854, other hospital; OR 0.539 95 % CI 0.435, 0.667) were independent predictors of a reduced odds of hospital mortality when adjusted for hospital length of stay.

Chronic renal failure (OR 0.833 95% CI 0.716, 0.968) and insulin dependent diabetes mellitus (OR 0.745 95% CI 0.608, 0.912), were independent predictors of the reduced odds of ICU mortality but not hospital mortality when adjusted for the natural logarithm of hospital length of stay.

The natural logarithms of ICU and hospital length of stay were significantly associated with the reduced odds of both ICU and hospital mortality in the multivariable models ($p \leq 0.001$).

Resistance and Mortality

In the unadjusted models of mortality, the presence of a resistant organism at the time of septic shock presentation was significantly associated with the increased risk of hospital (OR 1.214 95% CI 1.118, 1.318, $p \leq 0.001$) but not ICU mortality (1.063, 0.978, 1.156, $p \leq 0.151$). However the presence of a resistant organism at the time of septic shock presentation was not significantly associated with either ICU or hospital mortality when adjustment was made for relevant confounding variables in the multivariable models. Multivariable regression models of mortality are outlined in detail in Tables 5 and 6.

DISCUSSION

INTERPRETATION

Patient specific characteristics of resistance such as increased age, ventilator dependence, hospital acquired infection, surgical intervention, liver failure and insulin dependent diabetes were among expected results similar to those reported in previous studies [13,15,30-31,60]. Similarly, increased age, hospital acquired infection, and liver failure represented characteristics that were expected independent predictors of both the presence of a resistant organism and mortality and represent characteristics that should be examined further in future research.

Our study did show some unexpected findings.

Patients with a history of hypertension and leukemia demonstrated a reduced odds of presenting with a resistant organism at the time of septic shock. Although in itself there does not appear to be any biological plausibility describing why the presence of hypertension correlates with reduced risk of the presence of antibiotic resistance, hypertension is a known factor of many disease processes. This finding may be a result of a third potential confounding variable contributing to a protective effect of resistance that we did not adjust for in the model. Further, patients with Leukemia represent a population at increased risk for infection and greater implications as a result of resistant infections. As a result, this may represent a closely monitored population with targeted prophylactic and rational therapy combinations to prevent infection and resistance. It is known that a small portion of these patients may present with febrile neutropenia and negative cultures. However a positive culture was required for confirmed infection captured in

database and less than 1% of patients with leukemia had a suspected infection with the absence of a positive culture.

In assessing our secondary outcome of the effect of resistant organisms on mortality, our study demonstrated the natural logarithm of ICU and hospital length of stay were associated with a reduced odds of mortality. This result was suggestive of a survival bias, in which patients who died likely died early on in their ICU and hospital stay. Chi-Squared tests were conducted to assess the presence of a survival bias. Categories of ICU and hospital length of stay, in days, were assessed in relation to mortality. Over half of the population that died within the ICU died within the first 5 days of their ICU stay (54.9%). Overall, 72.5 % died within the first 10 days of their ICU stay. Similarly, 42.2% of patients who died in the Hospital, died within the first 5 days and overall 57.9% of patients died within the first 10 days of their hospital stay, representing a significant difference in distribution between those that died and those that survived. The results are further outlined in Appendix G. In context, the average length of stay was 10.49 ± 12.9 and 27.37 ± 35.7 days, respectively. The presence of a survival bias provides strong support to the importance of fitting length of stay in our mortality regression models. The collection of cultures and examination of resistant organisms was collected within 48 hours of patients being suspected of having septic shock. As a result, cultures and their resistance may not have been collected or captured for patients dying early on in their ICU or hospital stay.

It is important to note, that while the original protocol for the CATTS database required comorbid conditions be captured in a mutually exclusive manner we recognize there remains a small risk of collinearity among several comorbid conditions fit in our

regression models. We took several steps to address the risk of collinearity among the selected exposure variables. Tests for association between the exposures variables were conducted as well as an examination of collinearity matrix produced with each regression. Further, we examined regression models with and without the presence of variables that were thought to be closely related. There are several chronic comorbid conditions fit in our model that are captured as part of the APACHE II scoring system for illness severity. The presence of chronic comorbid conditions that were also captured in the APACHE II score were among the associations further examined for collinearity. There were no significant changes in the parameters of our models when fit without APACHE II or chronic comorbid conditions. We did not find any significant collinearity among the exposure variables in our models. The regression models assessing for collinearity are outlined further in Appendix F.

Resistance

Finally the presence of a resistant organism at the time of diagnosis of septic shock did not show any significant effect on mortality when adjusted for underlying comorbidities, severity of illness and length of stay. While other studies have indicated an association between resistance and mortality, their results focus on resistant organisms in the context of associations with decreased effectiveness of antibiotic therapy, improper dosing of antibiotics or inappropriate, delay in effective treatment, and increased requirement for surgery [15, 25]. We did not include antibiotic therapy in our final regression models as pre shock antibiotic use did not represent a significant association in the crude analysis. Further, pre hospital antibiotic therapy was not captured for this population and it was thought that due to the nature of septic shock diagnosis and that the majority of patients

were admitted through the emergency room, there would not be a significant antibiotic regime contributing to the presence of resistance at the time of septic shock.

However, we recognize the importance of this variable as described in previous literature and we will be including delay to appropriate therapy, and antibiotic specific details into future models to further assess the independent effect of resistance.

STRENGTHS

The study of antibiotic resistant organisms is complex. The major strength of this study is that the data has been controlled for the length of ICU and hospital stay and adjusted for the severity of the underlying illness and comorbidities as we acknowledge the confounding effect these parameters have on outcomes measures. Given the robust sample size (N=10800) this study allowed for the simultaneous examination of multiple epidemiological sub-groups in one model, while recognizing the ability to make safe interpretations of real associations between the variables included in the regression models. Moreover, the results from this study represent cases from twenty four centers across North America, lending to the generalizability of the results for this particular patient population.

LIMITATIONS

Given the retrospective nature of our study, several limitations may introduce bias. These include possible misclassification bias as a result of inaccuracies in charting, and possible failure to classify the primary outcome of a resistant organism accurately for all patients. The presence of a resistant organism was chosen as our primary outcome of interest relying on the accurate and similar assessment, identification, measurement and clinical documentation of these infection rates in the medical record.

Varying complexity of critically ill patients, including failing to capture ICU readmissions, could lead to the presence of selection bias when considering patient outcomes. Further, aggressiveness of care, antibiotic exposure and interventions aimed at reducing infection and resistance is likely to vary across North America. The era effect was not controlled for in this study. It is possible that awareness and practice changes relating to antibiotic resistance and infection control could vary over the 16 year span of data capture (1996-2012).

While our study attempted to control for underlying comorbidities and severity of illness, the database did not include comprehensive detail of pre-admission medication history or antibiotic exposure which has been shown in literature to be an important contributor to the development of resistant organisms.

The presence of a resistant organisms was selected as our primary outcome, defined as the presence of a resistant organisms at the time of septic shock diagnosis. With the absence of a temporal component of resistance onset in relation to exposure onset we are unable to draw causal relationships between epidemiological sub-populations and the development of resistant organisms. We can however provide results based on patient specific characteristics associated with the presence of resistant organisms.

CONCLUSION

In this retrospective study of septic patients admitted to North American intensive care units, age, liver failure, ventilator dependence, insulin dependent diabetes mellitus, neuromuscular disease and nosocomial acquired infection were patient specific predictors of the presence of antibiotic resistance organisms at the time of diagnosis of septic shock. Both elective and emergent surgery (vs medical diagnoses) was also associated with an

increased odds for the presence of an antibiotic resistant organism. However, leukemia and history of hypertension were associated with a lower odds of the presence of antibiotic resistance. The presence of a resistant organism was significantly associated with hospital but not ICU mortality when assessed independently of other factors. Our study showed no significant effect of the presence of antibiotic resistant organisms on ICU or Hospital mortality when adjusted for covariates such as age, underlying illness and severity of disease or length of stay. Further research should focus efforts on these patients groups for prevention of hospital acquired antibiotic resistance.

CONTRIBUTIONS

All of the authors contributed to the drafting and revision of the manuscript and approved the final version submitted for publication. Dr. Anand Kumar was responsible for the overall study design and the collection of data housed in the CATTS database. Demetrios Kutsogiannis and Tayne Hewer provided statistical analysis, manuscript preparation and review.

TABLES

Table 1. Baseline characteristics of critically ill patients with bloodstream infections

Characteristics	All (n=10,800)
Age, year (mean± SD)	62.8 ± 16.1
Male sex, n (%)	6041 (55.9)
BMI, kg/m2 (mean ± SD)[a]	28.2 ± 8.1
APACHE II score (mean ± SD)[b]	25.2 ± 8.1
Admission category, n (%)	
Medical	3023 (28.0)
Surgical	1678 (15.5)
Trauma (ER)	4106 (38.0)
Other ER	1043 (9.2)
Other ICU	499 (4.6)
Other Ward	451 (4.2)
Any Comorbidity	9650 (89.4)
Metastatic Cancer	1033 (9.6)
Immunosuppressive Therapy	1384 (12.8)
Organ Transplant	409 (3.8)
Neutropenia	453 (4.2)
Liver Failure	729 (6.8)
Hypertension	2731 (25.3)
Ventilator Dependent	49 (0.5)
Chronic Renal Failure	1632 (15.1)
Chronic Dialysis (PD, OR HD)	826 (7.6)
DM Insulin	866 (8.0)
Elective Surgery	1609 (14.9)
Emergent Surgery	705 (6.5)
ETOH	1479 (13.7)
Neuromuscular disease	227(2.1)
Acquisition of infection, n (%)	
Community acquired	6846 (63.4)
Hospital acquired	3954 (36.6)
Polymicrobial infection, n(%)[c]	469 (4.3)
Genus Group	
Escherichia coli	1605 (14.9)
Staphylococcus aureus	1274 (11.8)
Enterococcus spp	318 (3.0)
Klebsiella spp	566 (5.2)
Candida spp	441(4.1)
Streptococcus pneumonia	587 (5.4)
Pseudomonas aeruginosa	516 (4.8)
Enterobacter spp	247(2.3)
Alpha hemolytic streptococci	265 (2.5)
Other streptococci	144 (1.3)

BMI-body mass index; APACHE – Acute Physiology and Chronic Health Evaluation

[a] Excludes 5821 with missing BMI , [b] Excludes 633 with missing APACHE scores

[c] Patients with the presence of two or more resistant organisms

Table 2. Patient Specific Characteristics of Antibiotic Resistant Organisms χ2 and Fischer's Exact (2 Sided)

Variable	P Value
Comorbidity (Y,N)	0.000
Total Comorbidity ≥ 2	0.000
AIDS	0.207
Lymphoma	0.296
Leukemia	0.207
Metastatic Cancer	0.010
Immunosuppression	0.013
Organ Transplant	0.003
Neutropenia	0.116
Liver Failure – Hepatic Failure	0.045
NY Class 4 heart disease	0.372
CHF –Impaired cardiac function	0.161
ACS - Acute MI	0.776
IHD – Chronic Angina/CAD	1.000
Ht – Hypertension	0.003
Severe Chronic Obstructive Pulmonary Disease (COPD)	0.310
Chronic Obstructive Pulmonary Disease (COPD) medication requiring	0.342
Ventilator Dependent	0.012
CRF – Chronic renal failure	0.002
Chronic Dialysis	0.006
DM Meds	0.833
DM Insulin	0.003
Elective Surgery	0.000
Emergent Surgery	0.000
ETOH – Ethanol Alcohol Use	0.008
IVDU – IV Drug Use	0.392
Autoimmune Disease	0.852
Organic Brain	0.126
Thromboembolic - Pulmonary Embolus/DVT	0.930
Neuromuscular disease	0.016
Nosocomial Acquired Infection	0.000
Admission source (er,med,surgical,other er,other icu, other ward)	0.000

Table 2a. Patient Specific Characteristics of Antibiotic Resistant Organisms – Simple Logistic Regression

Age	0.032
APACHE	0.032

Table 3. Characteristics of infections in critically ill patients with bloodstream infections

Characteristics	All (n=10,800)
Resistant Organisms	
Presence of Any Resistant Organism n, (%)	3240 (30.0)
Presence of two resistant organisms n, (%)	469 (4.3)
Primary Resistant Organism n, (%)	
Escherichia coli	721 (6.7)
Klebsiella spp	589 (5.5)
Pseudomonas aeruginosa	553 (5.1)
Staphylococcus aureus	378 (3.5)
Eneterobacter	250 (2.3)
Enterococcus faecium	105 (1.0)
Streptococcus pneumonia	33 (0.3)
Infection Type	
Documented	9312 (86.2)
Suspected	1488 (13.8)
Source of infection, n (%)	
Pneumonia	4223 (39.1)
Urinary tract	1203 (11.1)
Vascular catheter	311(2.9)
Intra-abdominal	3107(28.8)
Skin & soft tissue	810 (7.5)

Table 4. Outcome characteristics of critically ill patients with bloodstream infections

Characteristics	All (n=10,800)
ICU Length of Stay, day (mean ± SD)	10.49 ± 12.9
Hospital Length of Stay, day (mean ± SD)	27.37 ± 35.7
Death, n(%)	
ICU mortality	4305 (39.9)
ICU mortality and ≥1 resistant organism	1325 (12.3)
Hospital mortality	5337 (49.4)
Hospital mortality and ≥1 resistant organism	1711 (15.8)
Death Due to Septic shock, n(%)	3330 (30.8)

Table 5. Multivariable logistic regression for independent predictors of the presence of antibiotic resistance at the time of septic shock diagnosis

Patient Characteristic	Univariable Model OR (95% CI)	P Value	Multivariable model OR (95% CI)	P Value
Age, year	1.003 (1.000-1.005)	0.032	1.002 (0.996-1.007)	0.013
APACHE	1.006 (1.000-1.011)	0.032	1.004 (1.001-1.007)	0.554
Nosocomial acquired Infection	1.878 (1.727-2.043)	≤ 0.001	1.699 (1.517-1.904)	≤ 0.001
AIDS	0.825 (0.620-1.099)	0.188	1.066 (0.789-1.439)	0.677
Leukemia	0.879 (0.724-1.069)	0.197	0.797 (0.636-0.998)	0.048
Metastatic Cancer	1.196 (1.044-1.371)	0.010	1.058 (0.914-1.225)	0.448
Immunosuppression	1.166 (1.034-1.316)	0.012	1.088 (0.929-1.274)	0.293
Organ Transplant	1.368 (1.114-1.681)	0.003	1.184 (0.938-1.496)	0.155
Neutropenia	1.175 (0.951-1.144)	0.114	1.135 (0.888-1.451)	0.312
Liver Failure	1.180 (1.006-1.385)	0.042	1.227 (1.028-1.463)	0.023
Chronic Heart Failure	0.905 (0.790-1.037)	0.151	0.874 (0.756-1.010)	0.069
Hypertension, high blood pressure medication required	0.863 (0.784-0.950)	0.003	0.863 (0.777-0.958)	0.006
Ventilator Dependent	2.072 (1.180-3.636)	0.011	2.088 (1.159-3.761)	0.014
Chronic Renal Failure	1.200 (1.073-1.343)	0.001	1.154 (0.979-1.360)	0.088
Chronic Dialysis	1.237 (1.065-1.437)	0.005	1.075 (0.866-1.334)	0.512
Diabetes Mellitus, insulin dependent	1.254 (1.083-1.452)	0.002	1.215 (1.036-1.424)	0.017
Elective Surgery	1.643 (1.472-1.834)	≤ 0.001	1.332 (1.166-1.521)	≤ 0.001
Emergent Surgery	1.538 (1.314-1.800)	≤ 0.001	1.244 (1.045-1.482)	0.014
ETOH	0.846 (0.748-0.957)	0.008	0.929 (0.810-1.065)	0.292
Organic Brain, dementia/multiple CVA	0.862 (0.715-1.039)	0.120	0.881 (0.724-1.073)	0.207
Neuromuscular Disease	1.407 (1.072-1.847)	0.014	1.540 (1.153-2.057)	0.003
ER	0.800 (0.734-0.872)	≤ 0.001	1.166 (0.926-1.468)	0.191
Medical	1.291 (1.180-1.412)	≤ 0.001	1.150 (0.915-1.446)	0.232
Surgical	1.367 (1.225-1.525)	≤ 0.001	1.055 (0.825-1.348)	0.670
Other ER	0.697 (0.601-0.809)	≤ 0.001	0.999 (0.766-1.303)	0.994
Other ICU	0.771 (0.627-0.948)	0.014	0.919 (0.680-1.243)	0.583

Hosmer and Lemeshow Goodness of Fit Test: $\chi^2 = 17.938$, df=8, p-value=0.022

Model $\chi^2 = 301.264$, df=26, p- value ≤ 0.001

Cox and Snell $R^2 = 0.029$

n= 10800

Dependent variable: Resistance=1 No resistance=0

Table 6. Multivariable logistic regression for independent predictors of ICU mortality

Patient Characteristic	Univariable Model OR (95% CI)	P Value	Multivariable model OR (95% CI)	P Value	Multivariable model [2] OR (95% CI)	P Value	Multivariable model [3] OR (95% CI)	P Value
Age, year	1.016 (1.014,1.019)	≤0.001	1.016 (1.013,1.020)	≤0.001	1.015 (1.012,0.019)	≤0.001	1.016 (1.012,1.019)	≤0.001
APACHE	1.127 (1.120,1.134)	≤0.001	1.121 (1.113,1.128)	≤0.001	1.116 (1.109,1.124)	≤0.001	1.095 (1.087,1.104)	≤0.001
Nosocomial acquired Infection	1.597 (1.469,1.723)	≤0.001	1.273 (1.134)	≤0.001	1.350 (1.200,1.518)	≤0.001	1.062(1.396,1.838)	≤0.001
AIDS	1.249 (0.970,1.609)	0.085	1.911 (1.410,2.591)	≤0.001	1.935 (1.420,2.636)	≤0.001	1.829(1.282,2.610)	0.001
Lymphoma	1.836 (1.49,2.264)	≤0.001	1.237 (0.956,1.601)	0.107	1.237 (0.952,1.607)	0.111	1.293(0.955,1.749)	0.096
Leukemia	2.115 (1.773,2.523)	≤0.001	1.132 (0.902,1.420)	0.284	1.088 (0.864,1.371)	0.472	0.951 (0.727,1.244)	0.712
Metastatic Cancer	1.408 (1.238,1.601)	≤0.001	1.297 (1.115,1.507)	0.001	1.233 (1.058,1.435)	0.007	1.180 (0.989,1.408)	0.067
Immunosuppression	1.787 (1.596,2.002)	≤0.001	1.263 (1.082,1.475)	0.003	1.212 (1.036,1.418)	0.016	1.157 (0.963,1.389)	0.120
Neutropenia	2.493 (2.055,3.024)	≤0.001	1.254 (0.969,1.623)	0.085	1.199 (0.932,1.559)	0.174	1.070 (0.786,1.456)	0.669
NYheart failure	1.677 (1.310,2.148)	≤0.001	1.648 (1.243,2.184)	0.001	1.679 (1.260,2.238)	≤0.001	1.557 (1.117,2.172)	0.009
Liver Failure	2.600 (2.22,3.035)	≤0.001	2.515 (2.103,3.008)	≤0.001	2.517 (2.098,3.020)	≤0.001	2.301 (1.865,2.839)	≤0.001
Chronic Heart Failure	1137 (1.004,1.287)	0.043	1.063 (0.919,1.230)	0.408	1.027 (0.886,1.191)	0.720	0.940 (0.791,1.117)	0.481
Hypertension	0.836 (0.765-0.915)	≤0.001	0.836 (0.750,0.932)	0.001	0.863 (0.773,0.964)	0.009	1.116 (0.984,1.267)	0.089
Ventilator Dependent	0.867 (0.489,1.567)	0.654	0.927 (0.480,1.793)	0.823	1.119 (0.575,2.178)	0.740	1.105 (0.530,2.300)	0.791
Chronic Obstructive Pulmonary Disease	1.129 (0.963,1.324)	0.134	1.015 (8.46,1.219)	0.869	1.061 (0.881,1.277)	0.534	1.082 (0.873,1.341)	0.471

Table 6 Continued. Multivariable logistic regression for independent predictors of ICU mortality

Patient Characteristic	Univariable Model OR (95% CI)	P Value	Multivariable model OR (95% CI)	P Value	Multivariable model [2] OR (95% CI)	P Value	Multivariable model [3] OR (95% CI)	P Value
Chronic Renal Failure	1.073 (0.964,1.194)	0.198	0.807 (0.710,0.918)	0.001	0.794 (0.697,0.904)	0.001	0.833 (0.716,0.968)	0.017
Diabetes, Medication	0.861 (0.781,0.949)	0.003	0.889 (0.790,0.999)	0.048	0.874 (0.777,0.985)	0.027	0.888 (0.774,1.019)	0.090
Diabetes, Insulin Dep	0.833 (0.721,0.963)	0.013	0.730 (0.613,0.869)	≤0.001	0.732 (0.614,0.872)	0.001	0.745 (0.608,0.912)	0.004
IV Drug Use	0.487 (0.352,0.674)	≤0.001	0.651 (0.438,0.967)	0.034	0.678 (0.455,1.010)	0.056	0.703 (0.453,1.090)	0.115
Pulmonary Embolus/DVT	0.766 (0.549,1.069)	0.117	0.836 (0.571,1.226)	0.360	0.806 (0.547,1.186)	0.273	0.876 (0.557,1.376)	0.565
Neuromuscular Disease	0.573 (0.428,0.769)	≤0.001	0.930 (0.666,1.298)	0.670	0.935 (0.669,1.305)	0.692	0.883 (0.604,1.289)	0.519
Elective Surgery	0.900 (0.807,1.004)	0.058	0.868 (0.753,1.001)	0.052	0.888 (0.769,1.025)	0.105	1.021 (0.864,1.207)	0.805
Admission Source								
ER	0.745 (0.688,0.807)	≤0.0010	0.743 (0.596,0.927)	0.008	0.657 (0.525,0.823)	≤0.001	0.567 (0.439,0.732)	≤0.001
Medical	1.66 (1.530,1.813)	≤0.001	1.045 (0.834,1.309)	0.702	0.955 (0.759,1.201)	0.692	1.000 (0.771,1.298)	0.999
Surgical	0.932 (0.837,1.037)	0.195	0.846 (0.663,1.078)	0.0176	0.775 (0.605,0.991)	0.043	0.897 (0.663,1.166)	0.372
Other ER	0.657 (0.573,0.754)	≤0.001	0.685 (0.530,0.885)	0.004	0.609 (0.470,0.790)	≤0.001	0.499 (0.371,0.670)	≤0.001
Other Ward	1.167 (0.965,1.412)	0.111	0.864 (0.640,1.166)	0.339	0.803 (0.592,1.089)	0.157	0.803 (0.569,1.133)	0.212
≥ 1 Resistant organism	1.063 (0.978,1.156)	0.151	0.963 (0.873,1.062)	0.451	0.970 (0.879,1.072)	0.554	1.004 (0.894,1.127)	0.950
LN ICU LOS	0.629 (0.602,0.657)	≤0.001			0.677 (0.643,0.712)	≤0.001		
LN Hosp LOS	0.277 (0.263,0.291)	≤0.001					0.278 (0.262,0.295)	≤0.001

n= 10800 Dependent variable: ICU Mortality = 1 ICU Survival = 0

1 Multivariable Model P <0.20 fit with resistance Hosmer and Lemeshow Goodness of Fit: χ 2 = 3.737, df=8, p-value=0.880; Model χ 2 = 2237.175, df=28, p ≤ 0.001; Cox and Snell R2 = 0.198

[2] Multivariable Model P <0.20 fit with resistance and LN ICU LOS Hosmer and Lemeshow Goodness of Fit: χ 2 = 52.6, df=8, p ≤ 0.001; Model χ 2 = 2472.21, df=29, p ≤ 0.001; Cox and Snell R2 = 0.216

[3] Multivariable Model P <0.20 fit with resistance and LN HOSP LOS Hosmer and Lemeshow Goodness of Fit: χ 2 = 133.04, df=8, p ≤ 0.001; Model χ 2 = 4941.73, df=29, p ≤ 0.001; Cox and Snell R2 = 0.385

Table 7. Multivariable logistic regression for independent predictors of hospital mortality

Patient Characteristic	Univariable Model OR (95% CI)	P Value	Multivariable model[1] OR (95% CI)	P Value	Multivariable model [2] OR (95% CI)	P Value	Multivariable model [3] OR (95% CI)	P Value
Age, year	1.023 (1.020-1.025)	≤0.001	1.025 (1.022,1.029)	≤0.001	1.025 (1.021,1.028)	≤0.001	1.026 (1.123,1.030)	≤0.001
APACHE	1.127 (1.120-1.134)	≤0.001	1.119 (1.111,1.126)	≤0.001	1.116 (1.109,1.124)	≤0.001	1.099 (1.091,1.107)	≤0.001
Nosocomial acquired Infection	2.082 (1.923-2.255)	≤0.001	1.563 (1.393,1.754)	≤0.001	0.324 (1.446,1.824)	≤0.001	2.040 (1.790,2.325)	≤0.001
AIDS	1.208 (0.938-1.555)	0.142	2.362 (1.737,3.212)	≤0.001	2.384 (1.750,3.247)	≤0.001	2.318 (1.650,3.257)	≤0.001
Lymphoma	2.236 (1.789,2.794)	≤0.001	1.832 (1.393,2.409)	≤0.001	1.834 (1.394,2.414)	≤0.001	1.987 (1.469,2.687)	≤0.001
Leukemia	2.430 (2.012-2.935)	≤0.001	1.445 (1.135,1.839)	0.003	1.413 (1.108,1.802)	0.005	1.271 (0.969,1.668)	0.083
Metastatic Cancer	1.537 (1.351-1.751)	≤0.001	1.436 (1.232,1.675)	≤0.001	1.387 (1.189,1.619)	≤0.001	1.363(1.149,1.617)	≤0.001
Immunosuppression	1.734 (1.545-1.946)	≤0.001	1.118 (0.954,1.310)	0.168	1.088 (0.928,1.276)	0.299	1.010 (0.845,1.208)	0.912
Neutropenia	2.613 (2.125-3.213)	≤0.001	1.286 (0.977,1.693)	0.073	1.243 (0.942,1.640)	0.124	1.089 (0.797,1.488)	0.591
Liver Failure	3.117 (2.630-3.694)	≤0.001	3.498 (2.875,4.257)	≤0.001	3.510 (2.879,4280)	≤0.001	3.359 (2.697,4.184)	≤0.001
New York Heart Failure	1.940 (1.498,2.513)	≤0.001	1.555 (1.154,2.093)	0.004	1.573 (1.166,2.123)	0.003	1.444 (1.035,2.015)	0.031
Chronic Heart Failure	1.249 (1.104-1.413)	≤0.001	1.097 (0.946,1.272)	0.221	1.073 (0.925,1.245)	0.353	1.022 (0.865,1.207)	0.800
Intermittent HD	1.135 (1.012,1.272)	0.030	1.094 (0.952,1.256)	0.204	1.095 (0.953,1.258)	0.200	1.073 (0.921,1.250)	0.364
Hypertension	0.766 (0.702-0.836)	≤0.001	0.690 (0.619,0.769)	≤0.001	0.702 (0.630,0.783)	≤0.001	0.816 (0.723,0.921)	0.001
Severe COPD	1.301 (1.11,1.524)	0.001	1.144 (0.952,1.375)	0.151	1.183 (0.983,1.423)	0.076	1.226 (0.999,1.504)	0.051
Ventilator Dependent	0.905 (0.516-1.588)	0.728	0.920 (0.477,1.772)	0.802	1.035 (0.536,1.998)	0.918	1.012 (0.499,2.054)	0.973

Table 7 Continued. Multivariable logistic regression for independent predictors of hospital mortality

Chronic Renal Failure	1.277 (1.149-1.419)	≤0.001	0.857 (0.722,1.017)	0.078	0.846 (0.712,1.004)	0.056	0.861 (0.710,1.042)	0.125
Chronic Dialysis	1.265 (1.097-1.459)	0.001	1.248 (0.994,1.566)	0.56	1.247 (0.993,1.565)	0.057	1.395 (1.085,1.793)	0.010
Diabetes, Medication Required	0.867 (0.789,0.953)	0.003	0.933 (0.832,1.047)	0.240	0.825 (0.824,1.038)	0.183	0.947 (0.833,1.076)	0.402
Emergent Surgery	1.227 (1.052-1.430)	0.009	1.118 (0.929,1.346)	0.237	1.167 (0.968,1.406)	0.105	1.339 (1.087,1.649)	0.006
IV Drug Use	0.425 (0.313,0.577)	≤0.001	0.648 (0.440,0.955)	0.028	0.665 (0.451,0.981)	0.040	0.674 (0.446,1.019)	0.062
Organic Brain, dementia	1.167 (0.988-1.379)	0.069	0.998 (0.821,1.213)	0.985	0.988 (0.812,1.202)	0.904	1.075 (0.864,1.337)	0.515
Neuromuscular Disease	0.561 (0.427-0.738)	≤0.001	0974 (0.705,1.346)	0.873	0.975 (0.706,1.346)	0.877	0.937 (0.657,1.337)	0.719
Admission Source								
ER	0.667 (0.617-0.721)	≤0.001	0.923 (0.802,1.062)	0.265	0.901 (0.783,1.038)	0.149	0.729 (0.622,0.854)	≤0.001
Medical	2.095 (1.922-2.283)	≤0.001	1.492 (1.305,1.705)	≤0.001	1.485 (1.298,1.699)	≤0.001	1.439 (1.239,1.672)	≤0.001
Other ER	0.524 (0.458-0.598)	≤0.001	0.741 (0.613,0.897)	0.002	0.723 (0.597,0.876)	0.001	0.539 (0.435,0.667)	≤0.001
Other ICU	0.884 (0.738-1.059)	0.181	1.048 (0.830,1.324)	0.691	1.102 (0.871,1.393)	0.419	0.961 (0.742,1.246)	0.766
≥ 1 Resistant organism	1.214 (1.118-1.318)	≤0.001	1.055 (0.957,1.164)	0.282	1.062 (0.962,1.172)	0.232	1.111 (0.996,1.240)	0.059
LN ICU LOS	0.734 (0.704-0.765)	≤0.001			0.780 (0.742,0.820)	≤0.001		
LN Hosp LOS	0.378 (0.363-0.394)	≤0.001					0.354 (0.335,0.373)	≤0.001

n= 10800 Dependent variable: Hospital Mortality = 1 Hospital Survival = 0

1 Multivariable Model P <0.20 fit with resistance Hosmer and Lemeshow Goodness of Fit: χ 2 = 8.901, df=8, p-value=0.351; Model χ 2 = 2697.025, df=28, p ≤ 0.001; Cox and Snell R2 = 0.233

[2] Multivariable Model P <0.20 fit with resistance and LN ICU LOS Hosmer and Lemeshow Goodness of Fit: χ 2 = 30.69, df=8, p ≤ 0.001; Model χ 2 = 2792.36, df=29, p ≤ 0.001; Cox and Snell R2 = 0.240

[3] Multivariable Model P <0.20 fit with resistance and LN HOSP LOS Hosmer and Lemeshow Goodness of Fit: χ 2 = 168.62, df=8, p ≤ 0.001; Model χ 2 = 4632.48, df=29, p ≤ 0.001; Cox and Snell R2= 0.366

FIGURES

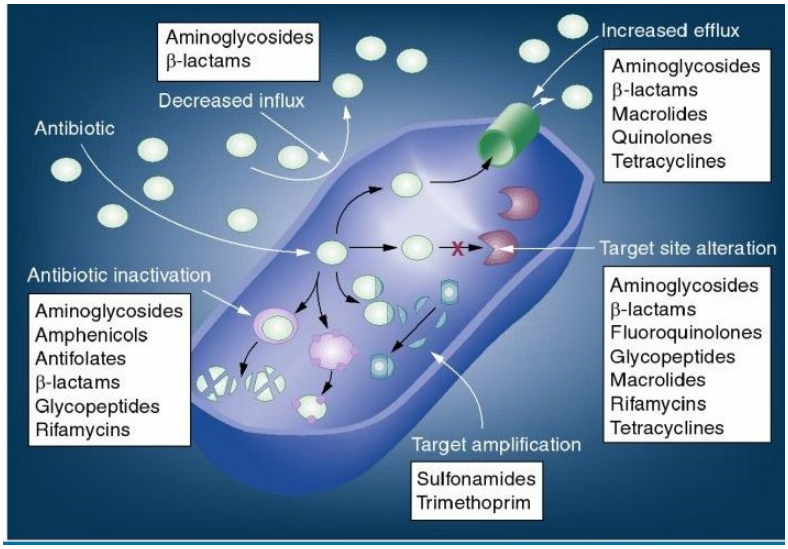


Figure 1: Mechanisms of Antibiotic Resistance in Bacteria. Taken from Schmieder R., Edwards R. Insights into Antibiotic Resistance Through Metagenomic Approaches Future Microbiol. 2012;7(1):73-89.

WORKS CITED

1. Maragakis LL, Perencevich EN, Cosgrove SE: Clinical and economic burden of antimicrobial resistance. Expert Rev Anti Infect Therapy. 2008 Oct;6(5):751-63
2. U.S. Congress, Office of Technology Assessment, Impacts of Antibiotic-Resistant Bacteria, OTA-H-629 (Washington, DC: U.S. Government Printing Office, September 1995). 1-187
3. Carmeli Y, Elipoulos G, Mozaffari E, Samore M. Health and Economic outcomes of vancomycin-resistant enterococci. Arch Intern Med. 2002 Oct 28; 162(19):2223-8.
4. Harris A, Torres-Viera C, Venkataraman L, DeGirolami P, Samore M, Carmeli Y. Epidemiology and clinical outcomes of patients with multiresistant pseudomonoas aeruginosa. Clinical Infectious Disease. 1999; 28(5) 1128-1133.
5. Cosgrove SE, QI Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance n staphylococcus aeureus bacteremia on patient outcomes: mortality, length of stay and hospital charges. Infection Control Hospital Epidemiology 2007; 28 (3) 273-279.
6. Blot S, Vandewoude K, Colardyn F. Nosocomial bacteremia involving acintobacter baumanni in critically ill patients: a matched cohort study. Intensive Care Medicine 2003; 29 (3) 471-475.
7. Zilahi G, Artigas A, Martin-Loeches I. What's new in multidrug-resistant pathogens in the ICU? Ann Intensive Care. 2016 Dec; 6(1):96.
8. Vincent J, Rello J, Marshall JC, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302:2323-29

9. Vincent JL, Marshall JC, Amendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Asessment of the worldwide burden of criticial illness: the intensive care over nations ICONS audit. Lancet Respiratory Medicine. 2014; 2:380-6.
10. Pogue JM, Kaye KS, Cohen DA, Marchaim D. Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens. Clinical Microbiology Infection. 2015; 21 (4) 302-312.
11. Martin-Loches I, Deja M, Koulenti D, Dimopolous G, Marsh B, Torres A, et al. Potentially resistant microorganisms in intubated patients with hospital acquired pneumonia: the interaction of ecology, shock and risk factors. Intensive Care Med. 2013:39 (4):672-81.
12. Harbarth S, Masuet-Aumatell C, Schrenzel J, Francois P, Akakpo C, Renzi G et al. Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling MRSA in critical care: an interventional cohort study. Critical Care 2006. 10:25
13. Russotto V, Cortegiani A, Graziano G, Saporito L, Raineri SM, Mammina C, Giarratoano A. Bloodstream infections in intensive care unit patients: distribution and antibiotic resistance of bacteria. Infection and drug resistance 2015: 8 287-296.
14. Johnson MT, Reichley R, Hoppe-Bauer J, Dunne WM, Micek S, Kollef M. Impact of previous antibiotic therapy on outcome of Gram-Negative severe sepsis. Critical Care Medicine 2011;29 (8): 1859-1865.
15. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009: 136: 1237-48.

16. Bone RC, Balk R, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for use of innovative therapies in sepsis: ACCP/SCCM Consensus conference Committee; American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101: 1644-1655.
17. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical Care Medicine 2006; 34: 1589-1596.
18. Burnham J, Lane M, Kollef M. Impact of sepsis classification and multidrug resistance status on outcome among patients treated with appropriate therapy. Critical Care Medicine 2016; 43(8):1580-1586.
19. Zilblerberg M, Shorr A, Micek S, Vazquez-Guillamet C, Kollef M. Multi-drug resistance, innapropriate initial antibiotic therapy and mortality in gram-negative severe sepsis and septic shock: a retrospective cohort study. Critical Care 2014; 18:596
20. Gould IM. The epidemiology of antibiotic resistance. International journal of antimicrobial agents 2008 Nov; 32 Suppl 1:S2-9.
21. Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, Goossens M M, Vaerenberg S, Hopkins S, Catry B, Monnet D L, Goossens H, and Suetens C. National Contact Points for the ECDC pilot point prevalence survey Collective, Hospital Contact Points for the ECDC pilot point prevalence survey Collective. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill. 2012;17(46): 20316.

22. Ventola, C. L. The Antibiotic Resistance Crisis: Part 1: Causes and Threats. Pharmacy and Therapeutics, 2015; 40(4), 277–283.
23. Antimicrobial resistance: global report on surveillance 2014. World Health Organization; 2014. Downloaded from http://www.who.int/drugreistance/documents/surveillancereport/en/. Accessed January 5, 2018.
24. Centers for Disease Control and Prevention. Antimicrobial resistance. September 19 2017; https://www.cdc.gov/drugresistance/about.html. Accessed December 8, 2017.
25. Munita, JM., Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016 April; 4 (2).
26. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clinical infectious disease 2006; 15, 42(Suppl 2):S82-9.
27. Sydnor ER, Perl, TM . Hospital Epidemiology and infection control in acute care settings. Clinical Microbiol review 2011; 24 (1):141-173.
28. Schmieder R., Edwards R. Review: Insights into antibiotic resistance through metagenomic approaches Future Microbiology. 2012 Jan; 7(1):73-89.
29. Dever LA1, Dermody TS. Mechanisms of bacterial resistance to antibiotics. Arch Intern Med 1991; 151(5):886-95.
30. Yelin I1, Kishony R2. Antibiotic Resistance. Cell 2018; 172(5):1136-1136
31. Ferguson JK. Preventing healthcare-associated infections: risks, healthcare systems and behaviors. Internal medicine Journal 2009; 29:574-581.

32. Taylor, M.E., Oppenheim BA. Hospital acquired infection in elderly patients. Journal Hospital Infection 1998; 28: 245-260.

33. Stanajit S., Indrawattana N Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens Biomed Res Int. 2016; 2475067. Accessed Jan 2018.

34. Public Health Agency of Canada. Antimicrobial resistance and use in Canada: A federal framework for action. CCDR: 2017 Nov 7; 40 (S-2) ISSN 1481-8531 Downloaded from http://healthycanadians.gc.ca/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/antimicrobial-framework-cadre-antimicrobiens-eng.php. Accessed December 9 2018.

35. Harris, A. Methodological Principles of Case-Control Studies That Analyzed Risk Factors for Antibiotic Resistance: A Systematic Review University of Maryland, Medical System Baltimore University of Maryland, Medical System Baltimore. Clinical Infect Dis. 2001 Apr 1; 32(7):1055-61. Accessed December 2018.

36. Valles J, Leon C, varez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). Clinical Infect Dis 1997;24(3):387-395.

37. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1994; 271(20):1598-1601.

38. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect 2006; 63(2):124-132.

39. Ramirez Mendoza JY, Daneman N, Elias MN, Amuah JE, Bush K, Couris CM, Leeb K. Infect Control Hosp Epidemiol. A Comparison of Administrative Data Versus Surveillance Data for Hospital-Associated Methicillin-Resistant Staphylococcus aureus Infections in Canadian Hospitals. 2017 Apr; 38(4):436-443. Accessed January 2018.
40. Daneman N, Shore K, Pinto R, Fowler R. Antibiotic Treatment Duration for Bloodstream Infections in Critically Ill Patients: A National Survey of Canadian Infectious Diseases and Critical Care Specialists. Int J Antimicrob Agents 2011;38: 480-485.
41. Weinstein MP, Towns ML, Quartey SM et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 1997;24(4):584-602.
42. Yamashita SK, Louie M, Simor AE, Rachlis A. Microbiological surveillance and parenteral antibiotic use in a critical care unit. Can J Infect Dis 2000;11(2):107-111.
43. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med 2003;163(8):972-978.
44. Dellit TH, Owens RC, McGowan JE, Jr. et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44(2):159-177.

45. Aarts MA, Brun-Buisson C, Cook DJ et al. Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empiric therapy improve outcome? Intensive Care Med 2007;33(8):1369-1378.
46. McDonald LC, Owings M, Jernigan DB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996-2003. Emerg Infect Dis 2006;12(3):409-415.
47. Wenzel RP. The antibiotic pipeline--challenges, costs, and values. N Engl J Med 2004;351(6):523-526.
48. Cassell GH, Mekalanos J. Development of antimicrobial agents in the era of new and reemerging infectious diseases and increasing antibiotic resistance. JAMA 2001;285(5):601-605.
49. Daneman N, Gruneir A, Bronskill SE et al. Prolonged Antibiotic Treatment in Long-term Care: Role of the Prescriber. JAMA Intern Med 2013;173(8):673-682.
50. Chastre J, Wolff M, Fagon JY et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290(19):2588-2598.
51. Blot, S., Cankurtaran, M., Petrovic, M., Vandijck, D., Lizy, C., Decruyenaere, J., Danneels, C., Vandewoude, K., Piette, A., Vershraegen, G., Van Den Noortgate, N., Peleman, R., Vogelaers, D (2009). Epidemiology and outcome of nosocomial bloodstream infection in elderly critically ill patients: A comparison between middle-aged, old, and very old patients. Crit Care Med. 2009 May;37(5):1634-41
52. Gavazzi G, Krause KH: Ageing and infection. Lancet Infect Dis 2002; 2:659–666

53. Laupland KB, Church DL, Mucenski M, et al: Population-based study of the epidemiology of and the risk factors for invasive Staphylococcus aureus infections. J Infect Dis 2003; 187:1452–1459

54. Yoshikawa TT: Epidemiology and unique aspects of aging and infectious diseases. Clin Infect Dis 2000; 30:931–933

55. Yoshikawa TT. Infectious diseases, immunity and aging: perspectives and prospects. In: Powers DC, Morley JE, Coe RM, eds. Aging, immunity and infection. New York: Springer, 1994:1–11.

56. Garcia A1, Delorme T2, Nasr P1. Patient age as a factor of antibiotic resistance in methicillin-resistant Staphylococcus aureus. J Med Microbiol. 2017 Dec;66(12):1782-1789. Accessed November 2018.

57. Cohen M, Salmasian H, Li J, Liu J, Zachariah P, Wright J, Freedberg DE. Surgical Antibiotic Prophylaxis and Risk for Postoperative Antibiotic-Resistant Infections. J Am Coll Surg. 2017; 225(5):631-638.e3. Accessed February 2018.

58. Brusselaers N., Vogelaers D.,Blotcorresponding S. The rising problem of antimicrobial resistance in the intensive care unit. Ann Intensive Care. 2011 Nov 23;1:47

59. Holmberg S, Solomon S, Blake P. Health and economic impacts of antimicrobial resistance. Rev Infect Dis. 1987 Nov-Dec; 9 (6):1065-78.

60. McGregor JC, Kim PW, Perencevich EN, Bradham DD, Furuno JP, Kaye KS, Fink JC, Langenberg P, Roghmann MC, Harris AD. Utility of the Chronic Disease Score and Charlson Comorbidity Index as Comorbidity Measures for Use in Epidemiologic

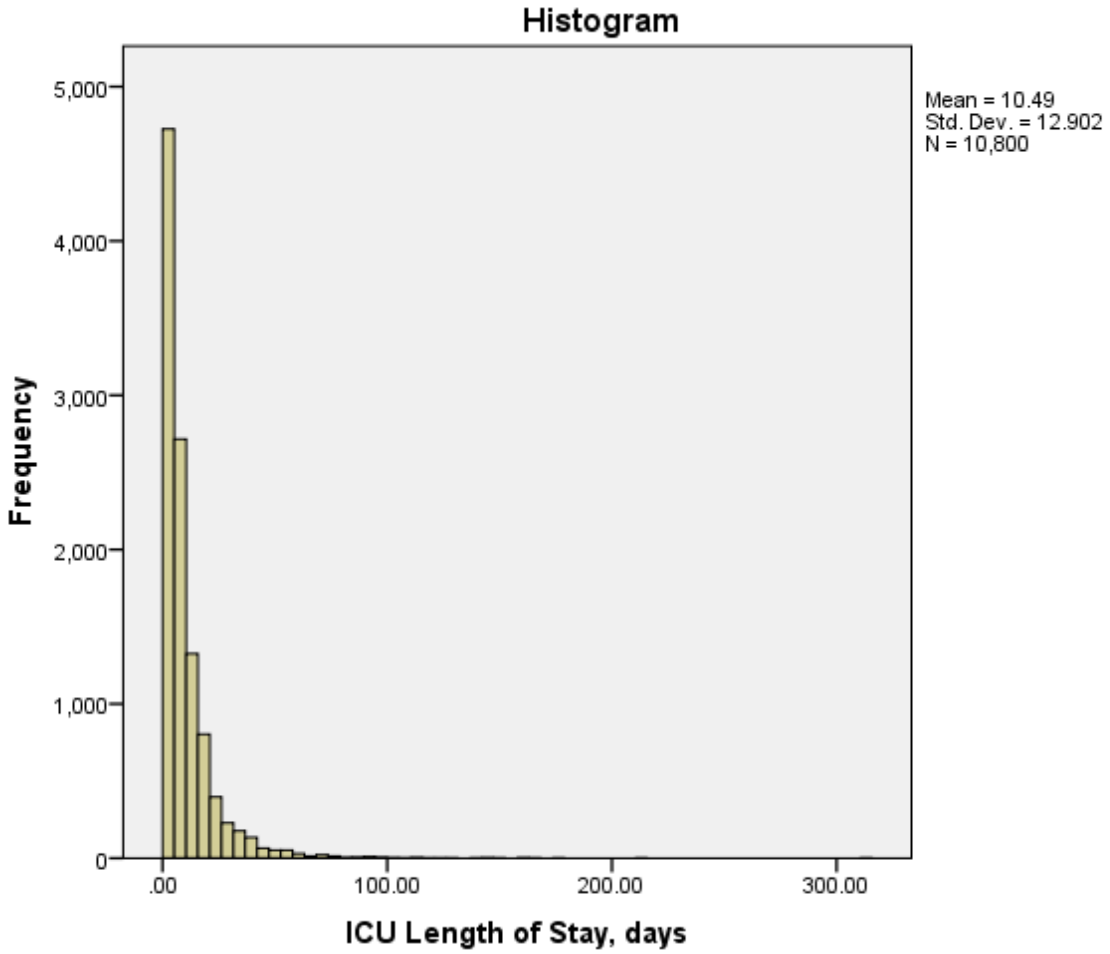
Studies of Antibiotic-resistant Organisms. American Journal of Epidemiology, Am J Epidemiol. 2005 Mar 1;161 (5):483-93.

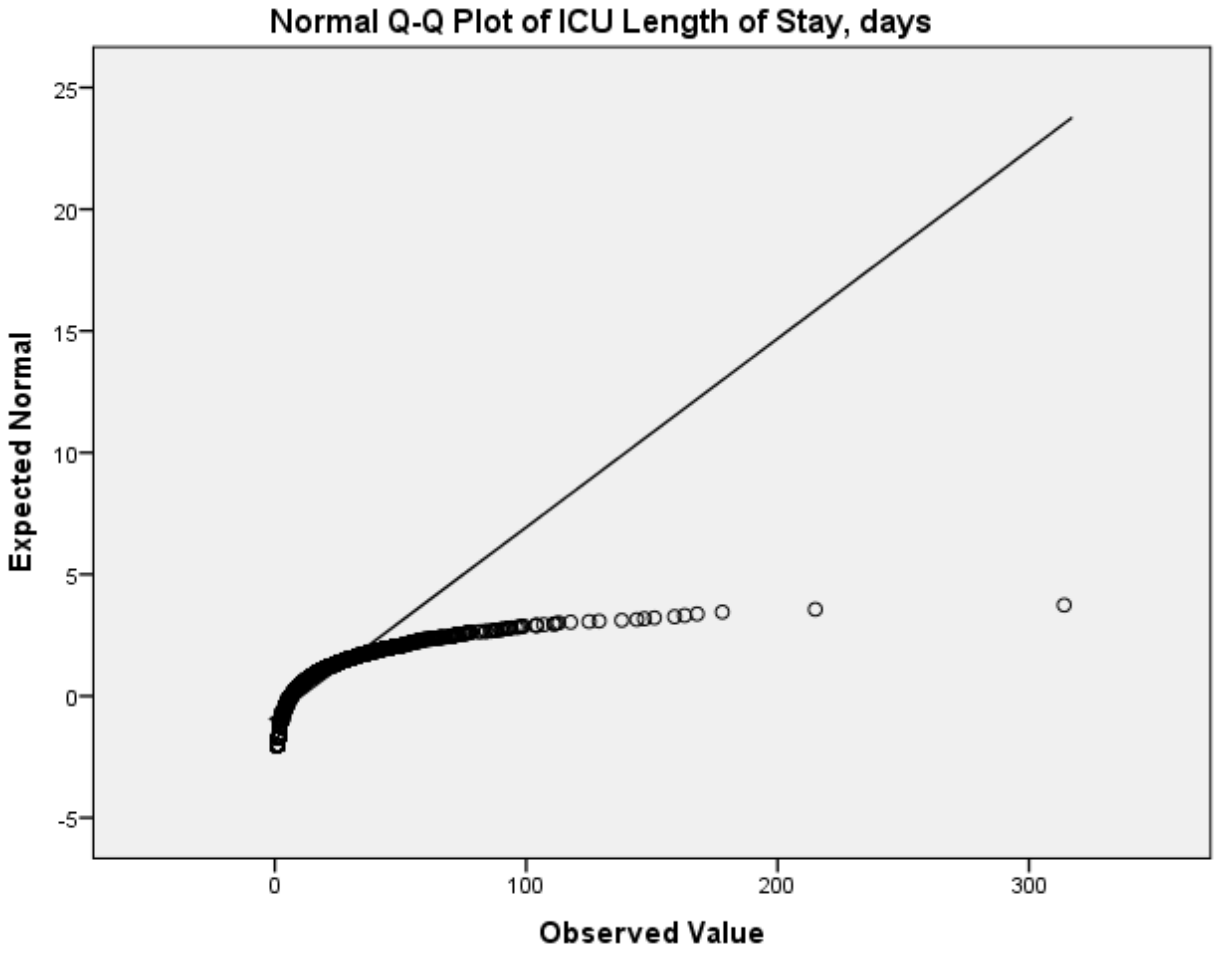
61. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulmé R, Lepage E, Le Gall R Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med. 2002 Feb; 28(2):108-21.
62. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991 Dec; 100(6):1619-36.
63. Pittet D, Thiévent B, Wenzel RP, Li N, Gurman G, Suter PM Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med. 1993; 19(5):265-72.
64. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis 2003; 36:1433-1437.
65. French GL. Clinical impact and relevance of antibiotic resistance. Adv Drug Deliv Rev 2005; 57:1514-1527.

Appendix A – Length of Stay Normality Testing

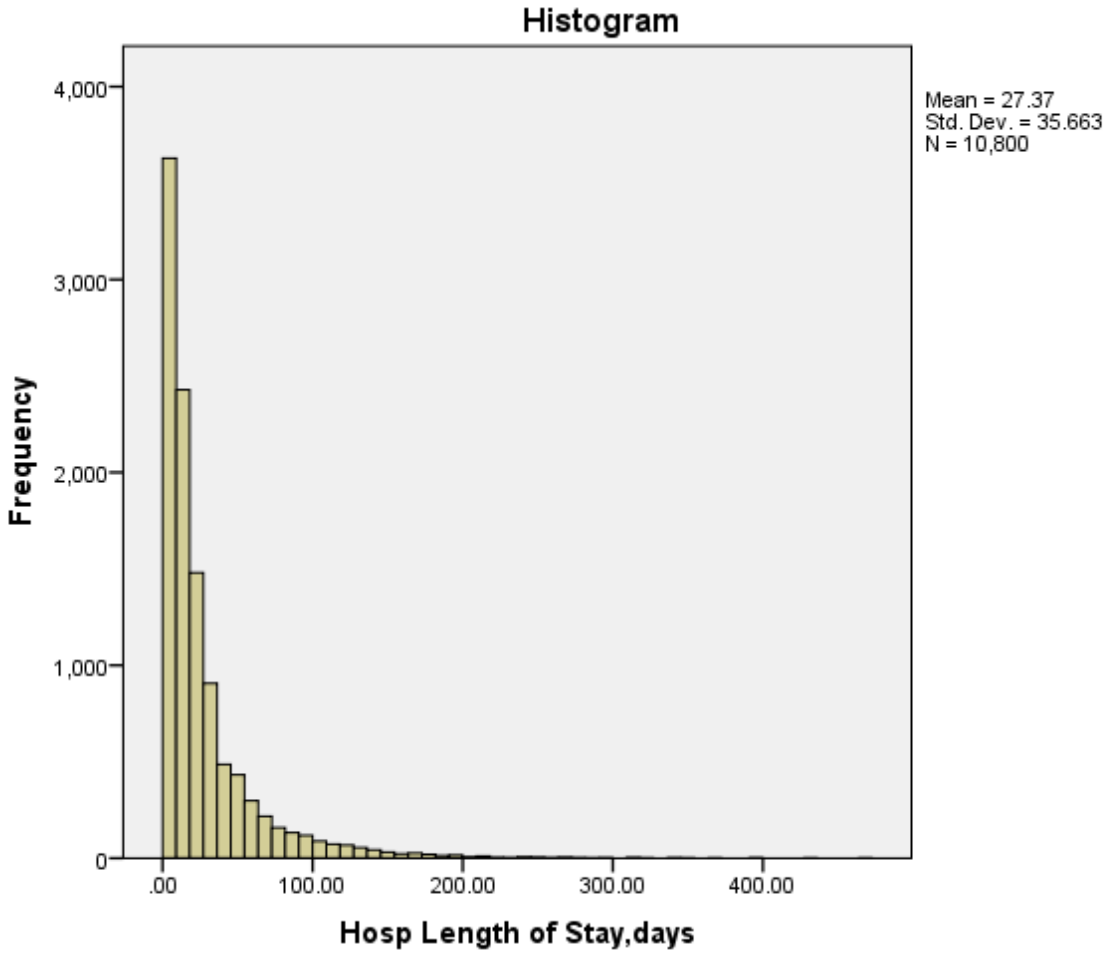
Normality Testing for ICU and Hospital Length of Stay

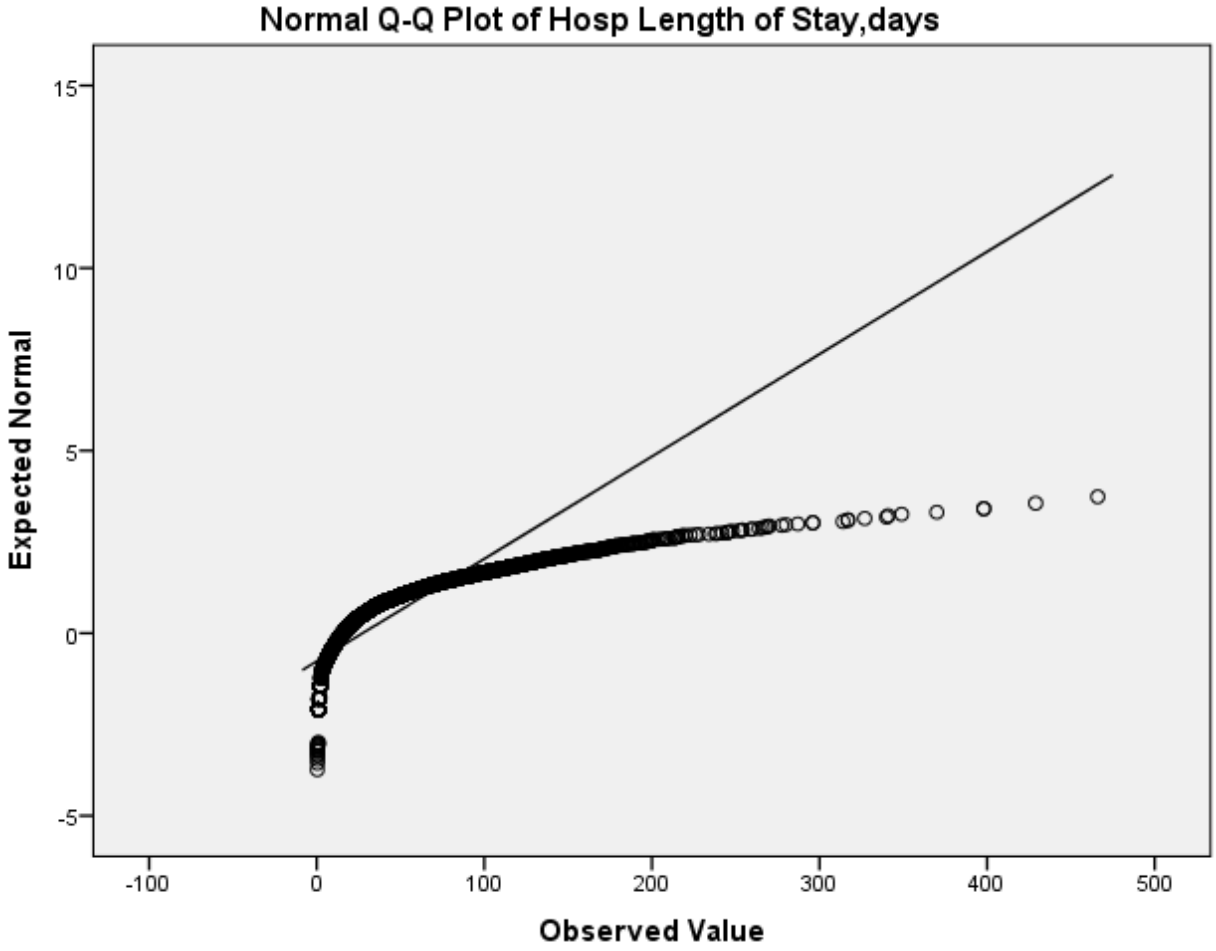
ICU Length of Stay, days




Normal Q-Q Plot of ICU Length of Stay, days
Expected Normal
25
20
15
10
5
0
-5
0
100
200
300
Observed Value

Hosp Length of Stay,days




Normal Q-Q Plot of Hosp Length of Stay,days
Expected Normal
15
10
5
0
-5
-100
0
100
200
300
400
500
Observed Value

Appendix B – Literature Search

Literature Search Strategy:

This review followed the STROBE guideline for reporting retrospective studies (BMJ 2007) as the following databases were searched: PubMed. EMBASE, Medline, Cochrane Databases of Systematic Review and Web of Science and included publications from 2000 to December 2017. The key phrases used in the search were: antimicrobial resistance, resistant infections, risk factors, epidemiology, complications, bloodstream infections, length of stay, liver failure, ventilator dependence, diabetes, neuromuscular disease, nosocomial, community acquired, predictors of resistance, elective and emergent surgery, elderly, injury severity, APACHE, and burden of resistance.

Once the search yielded articles on this topic, all articles from all databases were exported to RefWorks and Microsoft Word. Duplicate articles were then removed, and the remaining articles were screened by Dr. Kutsogiannis for relevance to the topic. Eligibility criteria for the review had special emphasis on variables that represented significant association with our primary and secondary outcomes in the multivariable statistical analysis.

Appendix C – Comorbidities

Comorbidities Captured in CATTS Database

1 AIDS (CDC criteria)
2 Lymphoma
3 Leukemia or multiple myeloma
4 Solid tumor with metastases
5 Immune suppression (chemotherapy or steroids > 10 mg prednisone/day)
5a organ transplant (BM, heart, lung, kidney, liver)-circle
6 Neutropenia (ANC <500/uL)
7 Hepatic failure (Bx proven cirhossis, portal HT, variceal bleed, encephalopathy)
8 NY Class 4 heart disease
8a Impaired cardiac function/reduced ejection fraction
8b Acute MI or acute unstable angina (by ECG, not enzymes)
8c Chronic angina/CAD/prior MI
8d Hypertension (high blood pressure; medication requiring)
9 COPD (previous ventilation, oxygen requiring, cor pulmonale, polycythemia,etc)
9a COPD medication requiring
10 Chronic ventilator dependence
11 Chronic renal failure (SCr 1.5 X normal)
12 Chronic dialysis (PD or HD)-circle
13 Diabetes (medication dependent)
14 Diabetes (insulin dependent)
15 Surgery (elective)
16 Major trauma/emergency surgery
17 Substance abuse (alchohol/IVDU)
18 Autoimmune disease: specify _____
19 Dementia/multiple CVA
20 Pulmonary embolus/DVT
21 Neuromuscular disorder (e.g. paralysis, mult sclerosis, Guillaine Barre, etc)

Appendix D – CATTS DATABASE

The Cooperative Antimicrobial Therapy of Septic Shock Database captures retrospective cases of patients who went into septic shock designed under the initial protocol aimed at examining the correlation between the time to appropriate antimicrobial and patient outcomes. Since the inception of the database, additional questions have been designed to answer other relevant clinical questions relating to this cohort of septic shock patients. This study utilizes the data captured under the initial protocol. The main CATTS database is managed through St. Boniface Research Center in Winnipeg, Canada. The overall principal investigator of the CATTS database is Dr. Anand Kumar.

Appendix E – Sample Size Calculation

A sample size calculation was conducted to describe the magnitude of our convenience sample. In a cohort of patients with septic shock, a sample size of N=1,108 would be required to estimate the relative risk of nosocomial acquired infection of 1.25 (10% precision), with a 2-sided alpha of 0.05, and power of 80%. Our convenience sample is ten-fold this sample size.

Appendix F – Collinearity Model, APACHE II Removed

Table 5a. Independent predictors of the presence of a resistant organisms at the time of septic shock – Collinearity Models

Patient Characteristic		Univariable Model OR (95% CI)	P Value	Multivariable model OR (95% CI)	P Value
Age, year		1.003 (1.000-1.005)	0.032	1.004 (*1.001*-1.007)	0.015
APACHE		1.006 (1.00-1.011)	0.032		
Nonsocomial acquired Infection		1.878 (1.727-2.043)	≤ 0.001	1.676	≤ 0.001
AIDS		0.825 (0.620-1.099)	0.188	1.020	0.896
Leukemia		0.879 (0.724-1.069)	0.197	0.757	0.013
Metastatic Cancer		1.196 (1.044-1.371)	0.010	1.061	0.413
Immunosuppression		1.166 (1.034-1.316)	0.012	1.107	0.193
Organ Transplant		1.368 (1.114-1.681)	0.003	1.188	0.142
Neutropenia		1.175 (0.951-1.144)	0.114	1.144	0.269
Liver Failure		1.180 (1.006-1.385)	0.042	1.235	0.015
Chronic Heart Failure		0.905 (0.790-1.037)	0.151	0.888	0.101
Hypertension		0.863 (0.784-0.950)	0.003	0.868	0.006
Ventilator Dependent		2.072 (1.180-3.636)	0.011	1.922	0.027
Chronic Renal Failure		1.200 (1.073-1.343)	0.001	1.143	0.102
Chronic Dialysis		1.237 (1.065-1.437)	0.005	1.066	0.551
Diabetes Mellitus, insulin dependent		1.254 (1.083-1.452)	0.002	1.212	0.014
Elective Surgery		1.643 (1.472-1.834)	≤ 0.001	1.374)	≤ 0.001
Emergent Surgery		1.538 (1.314-1.800)	≤ 0.001	1.312	0.002
ETOH		0.846 (0.748-0.957)	0.008	0.929	0.274
Organic Brain, dementia/multiple CVA		0.862 (0.715-1.039)	0.120	0.885	0.211
Neuromuscular Disease		1.407 (1.072-1.847)	0.014	1.568	0.002
	ER	0.800 (0.734-0.872)	≤ 0.001	1.192	0.123
	Medical	1.291 (1.180-1.412)	≤ 0.001	1.173	0.158
	Surgical	1.367 (1.225-1.525)	≤ 0.001	1.043	0.732
	Other ER	0.697 (0.601-0.809)	≤ 0.001	1.020	0.881

Appendix G – Survival Bias