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Improving Empiric Antibiotic Coverage for Gram-Negative Rod Infections Using Available Clinical Data

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Improving Empiric Antibiotic Coverage for Gram-Negative Rod Infections Using Available Clinical Data

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Health Policy and Management

by

Stefan Eisen Richter

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ABSTRACT OF THE DISSERTATION

Improving Empiric Antibiotic Coverage for Gram-Negative Rod Infections Using Available Clinical Data

by

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Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2018

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Infections due to antibiotic-resistant Gram-negative rods (GNRs) result in high associated mortality and frequently have poor treatment options. To determine risk factors for recovery on culture of antibiotic resistant GNRs, cases were retrospectively analyzed at a major academic hospital system from 2011-2016. Three separate classes of antibiotics were studied - colistin (analyzed separately for GNRs and for *Klebsiella Pneumoniae*), carbapenems (analyzed separately for ertapenem and anti-Pseudomonal carbapenems), and aminoglycosides (analyzed separately for gentamicin/tobramycin and amikacin). In each case, bivariate associations were determined and used to develop multivariate models predicting the presence of resistance to the chosen antibiotic. Models had c-statistics ranging from 0.63 to 0.89. Common predictors included male gender, medical comorbidities, transfer from another healthcare facility, indicators of mechanical ventilation or tracheostomy, and recent antibiotic exposure. We then compared two strategies of treating empirically with either meropenem or colistin

and performed sensitivity analyses to determine which strategy was preferable in terms of cost (low acuity) and avoidance of mortality (high acuity strategy) under several willingness-to-pay thresholds. Under base case assumptions, the meropenem-first strategy dominated in low acuity patients at a meropenem resistance rate of up to 10.9%. In high acuity patients, the colistin strategy was preferable with a willingness-to-pay per avoided death as low as $46,231; at $468,750 per avoided death, the colistin-first strategy was preferable with meropenem resistance rates as low as 5.5%. The model predicting likelihood of resistance to anti-Pseudomonal carbapenems can provide critical information in determining the optimal initial empiric antibiotic strategy.

The dissertation of Stefan Eisen Richter is approved.

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2018

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Presentations

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Richter SE, Roberts K, Preston I, Shah A, Shah A, Hill N. Diastolic Pulmonary Artery Pressure – Pulmonary Artery Occlusion Pressure Difference Predicts World Health Organization (WHO) Group 2 Pulmonary Hypertension. Presentation at: American Lung Association of New England 66th Annual Conference, Newton, Massachusetts, April 6, 2011.

Chapter 1 - Introduction

The objective of this research is to improve antibiotic prescribing patterns in the inpatient setting by modeling risk for infections in which broad spectrum antibiotic use is warranted. In the US there are currently approximately 2 million annual cases of infections with multi-drug resistant organisms (MDROs), with ~23,000 attributable deaths and $50 million in directly attributable costs.[1] In 2013 the CDC released a report on antibiotic resistance threats outlining the urgency of the problem of MDROs in our healthcare system, and recommending four specific courses of action: (1) preventing infections and the spread of resistance, (2) tracking resistant bacteria, (3) improving the use of antibiotics, and (4) promoting the development of new antibiotics and tests.[2] This project aims to address goals two and three, tracking MDRO infections within hospital systems and predicting the risk for MDROs in a patient presenting to medical care. By addressing these goals, we seek to improve the likelihood that the initial choice of antibiotic for empiric treatment appropriately treats the most likely infection.

Initial antibiotic selection for patients remains a challenge. Appropriate initial antibiotic therapy can decrease mortality[3-9] and hospital length of stay,[6,10-14] while overuse of broad-spectrum antibiotics has been linked with increased prevalence of MDROs.[15-19] Prior modeling of risk for MDRO infection has typically focused on risks for specific organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA),[20,21] extended-spectrum beta lactamase-producing (ESBL) *E. coli* or *Klebsiella* species,[22-24] MDR *Pseudomonas aeruginosa*,[25,26] carbapenem-resistant Enterobacteriaceae (CRE),[18,27,28] or vancomycin-resistant enterococcus (VRE),[29] or has focused on specific patient populations, such as stem cell transplant recipients[30] or ICU patients.[31]

The most frequently used current decision rules for initial antibiotic therapy for a specific condition are the guidelines for treatment of pneumonia, which breaks patients

into either community acquired pneumonia (CAP) or healthcare associated pneumonia (HCAP); this categorization has been criticized as insufficiently sensitive and specific for guiding clinical decisions.[32-36] A recent study with a derivation cohort of only 200 patients presenting with pneumonia demonstrated that the implementation of a human-usable scoring system based on their data would have improved the accuracy of the initial antibiotic choice substantially over the existing rule (AUROC 0.88 vs. 0.72).[37]

Aside from pneumonia, very few studies have attempted to create an integrated algorithm for determining antibiotic choice on the basis of a general condition as opposed to a specific organism. After a culture is drawn, information regarding the morphological characteristics of the infectious organism (gram negativity vs. positivity, shape of the bacterium) are typically available fairly rapidly, typically within 48 hours. Identification of the species will follow after that, and then sensitivities to specific antibiotic classes afterwards. In some cases, full information regarding antibiotic sensitivities is not available for nearly a week after cultures are first drawn, and choice of antibiotics is made in the absence of full information. This work aims to improve the process of antibiotic selection for gram negative rod (GNR) infections, focusing primarily on empiric treatment for undifferentiated infections. Better-informed decision making at this point can decrease the time to initiation of appropriate antibiotic therapy, and thereby potentially improve outcomes.[8,9]

The work of this thesis comprises two distinct and related projects. The first project, “Identification of risk factors for development of resistance to specific antibiotics”, focuses on modeling the probability that the organism of interest (whether an undifferentiated GNR or a specific bacterial species) is non-susceptible to a chosen antibiotic. Three classes of antibiotics have been chosen for this step - colistin (polymyxin E), carbapenems, and aminoglycosides. While these are not exhaustive of the classes of antibiotics used to treat GNR infections, they are second- and third-line

agents for the treatment of GNR infections, and development of resistance to any one of these agents is a clinically significant event. In the cases of colistin and carbapenems, prior papers have attempted to determine risk factors for the development of resistance to these agents but have not created a clinically meaningful scoring system; colistin is significantly less studied than carbapenems, and very few studies have looked at aminoglycosides. A summary of the selection process for the multivariate models for these three antibiotic classes is provided in the relevant papers; a more in-depth explanation of the selection process can be found for colistin, carbapenems, and aminoglycosides in Appendices A, B, and C, respectively.

The second project, “The cost-effectiveness of meropenem versus colistin in the initial empiric treatment of low and high acuity patients presenting with undifferentiated infections”, integrates information from Project 1 with information regarding cost and outcomes to attempt to create an algorithm guiding treatment of GNRs prior to final determination of antibiotic sensitivities. This single paper describes the analysis of a decision regarding initial antibiotic therapy made in the absence of culture data, specifically whether meropenem or colistin is a better first-line choice of antibiotic. The paper examines two scenarios, corresponding to low and high acuity patients. In the low acuity scenario there is no substantially increased risk for mortality, and the analysis focuses exclusively on determination of the lower-cost option. In the high acuity scenario there is a substantial increase in mortality risk associated with inappropriate initial antibiotic therapy, and a cost-effectiveness analysis is performed looking at the cost per avoided death. In both cases, the analysis supports the use of the algorithms developed in Project 1 to determine the pre-test probability of resistance to various antibiotics.

Chapter 2 - Overview of Project 1

Dataset

The dataset for this project includes all patients with positive cultures from any source over a six-year period at both UCLA Hospitals. Ronald Reagan UCLA Medical Center is a 520-bed tertiary care center with five adult intensive care units totaling 109 beds, Santa Monica-UCLA Medical Center has 266 beds total with 22 mixed intensive care beds in a single unit. Both are part of UCLA Health and service patients with solid organ and bone marrow transplants, cancer, and various medical and surgical conditions. The Integrated Clinical and Research Data Repository (xDR) serves as a warehouse for all clinical data in the UCLA system since the implementation of the electronic health record (EHR) in 2006. The original dataset contains information from all admissions with start dates from January 2006 through November 2016 to either hospital with patients ≥18 years of age and at least one positive culture from any source (blood, urine, sputum, wound cultures, or other fluids). However, the majority of information is incomplete prior to 2011, as additional fields were added to the EHR over time, and certain key variables are not available for earlier cases. As such, the analysis for these studies focuses on patients admitted in 2011 and beyond.

Routine microbiology susceptibility testing was performed by the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method (MD), using panels prepared in-house.

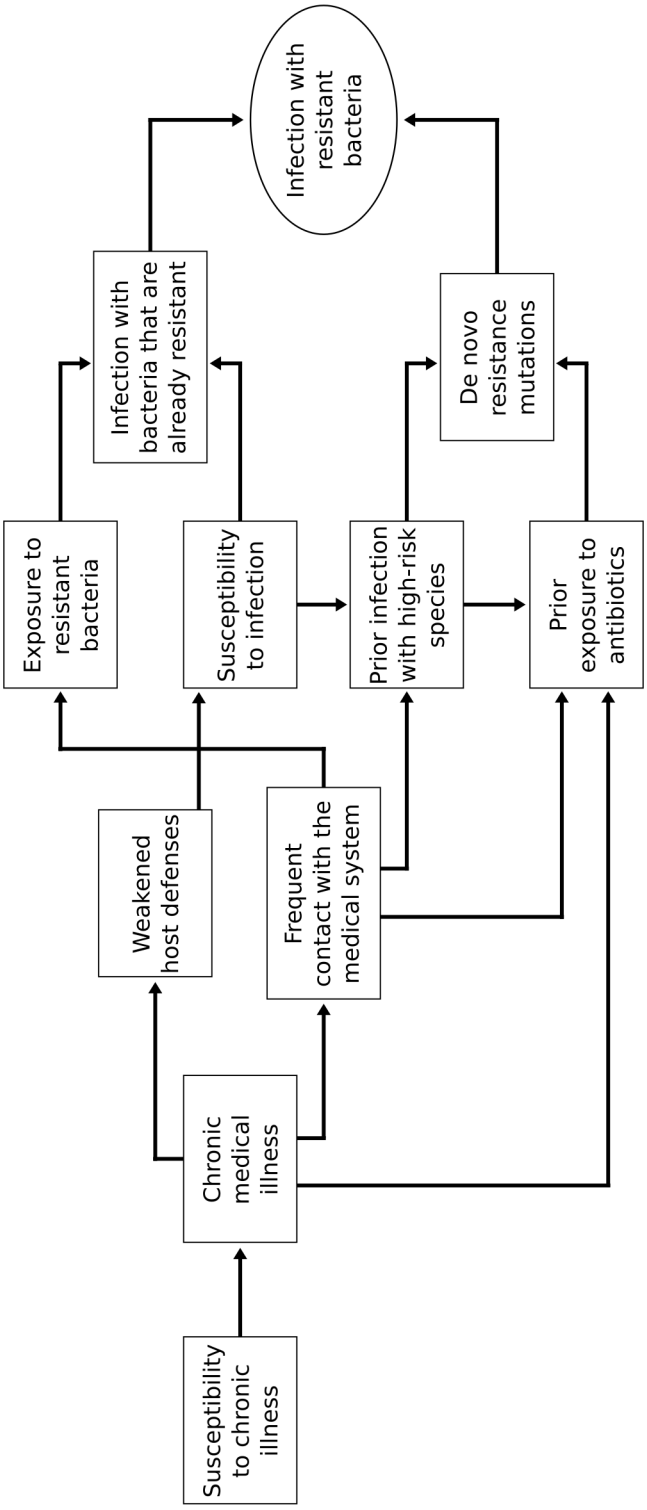
Predictor variables were chosen on the basis of prior studies, as well as those with biologic plausibility that were easily obtainable from the medical record. Data collected for each patient included admission hospital, days since start of admission, location prior to admission (home vs. long-term care facility), demographic information, medical comorbidities (grouped into categories based on Elixhauser score

designations),[27] laboratory results from the date of the culture, vital signs on the date of the culture (maximum temperature, heart rate, and respiratory rate, and minimum blood pressure), vital signs from initial hospital presentation, oxygen/ventilation method, presence of a tracheostomy and urinary catheter, infection source, and prior infection with carbapenem-resistant GNRs. Administration of antibiotics and other selected medications (pressors, probiotics, blood products, hematopoetic agents, inhalers, acid suppressants, and TPN) was coded as the number of days since last receipt of the medication, Winsorized to a maximum value of 100 (received within 24 hours of the time of culture = 0, never received was coded as 100 days since receipt). The variable "antipseudomonal carbapenem" refers to receipt of meropenem, imipenem, or doripenem. "Anti-MRSA" agents includes any agent with specific activity against MRSA, including vancomycin, linezolid, and daptomycin. The construct of advanced ventilatory support includes patients receiving either non-invasive or invasive mechanical ventilation.

In cases where laboratory tests were not performed before cultures were sent (typically at the beginning of a patient's admission), the first set of laboratory results were used for that patient, provided they were performed on specimens collected within 24 hours of culture positivity. For laboratory tests not typically performed daily (e.g., liver function tests, measures of coagulation, and protein/prealbumin), the most recent result within a 48-hour period was used.

Conceptual Model

Figure 2-1: Conceptual Model for Project 1



Model Overview

There are two pathways for acquisition of drug-resistant bacteria - infection with an isolate with pre-existing resistance, or development of resistance in pre-existing high-risk bacterium. Typically these high-risk bacteria (e.g. *Pseudomonas*, *Klebsiella*, and *Acinetobacter* species) colonize patients who are chronically ill and either have indwelling devices such as tracheostomies or urinary catheters, or abnormal physiologies, such as bronchiectasis (or other chronic lung diseases) or vascular abnormalities; however, in some cases, patients may develop colonizing high-risk bacteria in an absence of extraordinary risk factors. In order to develop resistance among colonizing bacteria, the patient must have both infection with high-risk bacteria and exposure to antibiotics capable of leading to resistance. Exposure to and infection with bacteria that are already resistant typically occurs through contact with the medical system, more frequently in long-term care than acute care. As such, susceptibility to infection and amount of contact with the medical system are key risk factors for both pathways leading to acquisition of resistant bacteria. Chronic medical illness drives both susceptibility to infection and contact with the medical system, and it also can lead to receipt of antibiotics even in the absence of prior clinically significant infections, particularly in the case of empiric antibiotic therapy for unexplained clinical decompensation. Chronic medical illness is the most common cause for increased susceptibility to infection, typically through use of immunosuppressive medications, chronic inflammatory states, or depletion of host defenses through malnutrition. Chronic medical illness is typically preceded by susceptibility to such illness, such as demographic risk factors or use of harmful substances such as tobacco and alcohol.

An explanation of the constructs and associated data fields follows.

<u>Susceptibility to chronic illness</u>

Associated data fields: Date of birth/age, Gender, Race/ethnicity, Social history

Susceptibility to chronic illness is the construct that is likely least-directly related to the ultimate outcome, because its effect is mediated by so many intermediate constructs. However, many of those intermediate constructs are not easily proxied by the available data, so there is still some role for demographic information and other basic risk factors in the model.

Chronic medical illness

Associated data fields: Location prior to admission, Location within hospital, Comorbidity list, Vital signs, Laboratory values, Indwelling devices, Medications received

Chronic medical illness is a complicated construct, in part because it is downstream of essentially every other construct in the model. Some information regarding chronic medical illness is directly accessible from the medical record in the form of listed medical comorbidities and recently received medications, but these do not fully capture a patient's clinical state, as two patients with identical comorbidity lists can be in very different states of health. Several other pieces of information inform a patient's general health state, many of which are related to acute illness; after controlling for comorbidities and infection type, the severity of an acute illness can serve as a proxy for a patient's general debility, as healthier patients will get less sick from similar illnesses. As such, most of the data associated with severity of the current episode of illness can be used to gain information regarding a patient's state of chronic medical illness.

Weakened host defenses

Associated data fields: Medications received

While the majority of weakened host defenses stem directly from medical comorbidities, some patients are on immunosuppressive medications (such as steroids, chemotherapy, antibodies, or biologic therapy) that can directly increase susceptibility to infection. Since these immunosuppressive therapies are typically continuous

medications given over months to years, current receipt of an immunosuppressive medication is likely highly correlated with prior immunosuppressive therapy.

Frequent contact with the medical system

Associated data fields: Location prior to admission, Indwelling devices

Location prior to admission (i.e. whether the patient is presenting from a long-term acute care facility/LTACH, another hospital, or from home) is the most direct proxy available in the dataset for determining whether or not a patient is chronically hospitalized. Direct admission from another facility captures the most chronically hospitalized population, but fails to capture several scenarios, including patients who spent time in an LTACH, but were discharged home before admission, or patients with frequent outpatient contact, such as those on chronic hemodialysis. Presence of a chronic tracheostomy (present on admission) is also indicative of persistent contact with the medical system. Chronic medical illness is likely the best remaining proxy for frequent contact with the medical system, as illustrated in the model above, and much of the influence of chronic medical illness on the final outcome is likely mediated by the frequency of contact with medical facilities.

Exposure to resistant bacteria

Associated data fields: None

The dataset does not contain any information directly pertaining to exposure to resistant bacteria. This could theoretically be accessed by looking at the antibiogram data for facilities in which patients were seen prior to admission, or microbiology data from roommates/family members of the patients, but these data are not available in the xDR dataset. As such, this important construct is incompletely measured, and predominantly proxied by the upstream factors of contact with the medical system and medical comorbidity.

Susceptibility to infection

Associated data fields: Social history, Location within hospital, Vital signs, Laboratory values, Indwelling devices

Susceptibility to infection matters most at the time of exposure to resistant bacteria, which usually happens at other facilities, outside the purview of this dataset. However, the dataset contains several fields that are potentially relevant to susceptibility during hospitalization at UCLA, namely measures of current acuity of illness. To a certain extent, as mentioned above, current acute illness is a marker of prior chronic illness and susceptibility, and this is this primary mechanism by which markers of acute illness can help proxy for susceptibility. Additionally, chronic indwelling devices increase the risk of infection via bypassing host defenses. However, the majority of information regarding susceptibility to infection will be obtained through information about chronic medical illness.

Prior infection with high-risk species

Associated data fields: Microbiology results

This is difficult construct to access, as information prior to a given admission is not accessible from the information provided. Since a large amount of this information is missing, it must largely be inferred from upstream constructs. Culture data for a given patient during the index or prior hospitalization at UCLA is available, as are sensitivities. In each paper, the presence of prior infection with a GNR resistant to other classes of antibiotics (aside from the one being studies) is analyzed as a risk factor.

Prior exposure to antibiotics

Associated data fields: Medications received

Since the dataset only includes inpatient data, there is information regarding prior antibiotic receipt that is not captured in these studies. In this dataset, exposure to antibiotics is operationalized as number of days since receipt of a particular class of antibiotic, Winsorized to a maximum value of 100 days (a value of zero means the

antibiotic in question was received on the day of culture, as long as this was not the first day the patient received the antibiotic). The receipt of probiotics may also serve as a proxy for prior antibiotic receipt, as many patients are placed on probiotics prophylactically while they are on other antibiotics, and potentially continued on probiotics after the end of their antibiotic therapy.

Infection with previously resistant bacteria/ De novo resistance mutations

Associated data fields: None

These constructs represent the two theoretical pathways towards the outcome, and are not directly measured. Since the outcome is agnostic to the source of resistant bacteria, the proportion of patients arriving via each pathway is indeterminate. These constructs are not operationalized in the dataset, and serve as mediators for the effects of upstream risk factors on the final outcome.

Infection with resistant bacteria

Associated data fields: Microbiology results

The outcome in each paper is the presence of resistance to the studied antibiotic on a given culture, taken directly from the microbiology results in the dataset. Resistance is determined by current CLSI standards.

Table 2-1: Measures

Measure	Data Source	Notes	Construct
Date of birth/age	Single text field in CareConnect	Difference between DOB and admission date	Susceptibility to medical illness
Gender	Single text field in CareConnect		Susceptibility to medical illness
Race/Ethnicity	Single text field in CareConnect	Combined field/data	Susceptibility to medical illness
Social history	Multiple separate fields in CareConnect	Includes smoking history, alcohol intake, and other drug use	Susceptibility to medical illness, Susceptibility to infection
Location Prior to Admission	Single text field in CareConnect	Used to determine if the patient was admitted from a long-term care facility	Chronic illness, Contact with the medical system
Location Within Hospital	Single text field in CareConnect	Used to determine if the patient is in an ICU or regular ward	Chronic illness, Susceptibility to infection
Comorbidity list	Constructed by applying the Elixhauser Score categories[27] to the available list of comorbidities	Elixhauser comorbidity index is used to calculate expected in-hospital mortality, and also serves to group similar diagnoses	Chronic illness
Vital signs	Extractable en bloc from CareConnect	Includes height, weight, blood pressure, pulse, temperature, respiratory status, oxygen saturation	Chronic illness, Susceptibility to infection
Indwelling devices	Extractable by looking at device-associated procedures in CareConnect	Indwelling urinary catheter, tracheostomy, ventilator. No reliable information on central lines/indwelling venous catheters.	Chronic illness, Susceptibility to infection, Contact with the medical system
Laboratory results	Extractable en bloc from CareConnect	Complete blood count, basic chemistries, coagulation studies	Chronic illness, Susceptibility to infection
Medications received	Extractable en bloc from CareConnect	Grouped by class of medication; medications that serve similar functions are treated as the same medication	Chronic illness, Weakened host defenses, Prior exposure to antibiotics
Microbiology results	Extractable en bloc from CareConnect	All positive cultures from any source, includes organism and sensitivity to specific antibiotics	Outcome, Prior infectious exposure

Chapter 3 - Risk factors for developing colistin resistance among Gram-negative rods and *Klebsiella pneumoniae*.

Stefan E. Richter, Loren Miller, Daniel Z. Uslan, Douglas Bell, Karol Watson, Romney Humphries, James A. McKinnell

Abstract

Infections due to colistin-resistant Gram-negative rods (ColR-GNR), and colistin-resistant *Klebsiella pneumoniae* (ColR-KP) in particular result in high associated mortality and poor treatment options. To determine risk factors for recovery on culture of ColR-GNR and ColR-KP, two key decision time points for choosing antimicrobial therapy corresponding to Gram stain and species identification results, cases were retrospectively analyzed at a major academic hospital system from 2011-2016. After excluding bacteria that are intrinsically resistant to colistin, a total of 28,512 GNR isolates (4,557 *K. pneumoniae*) were analyzed, 128 (0.45%) of which were ColR (i.e., MIC >2 ug/mL), including 68 (1.49%) of which were ColR-KP. In multivariate analysis, risk factors for ColR-GNR were neurologic disease, residence in a skilled nursing facility prior to admission, receipt of carbapenems in the last 90 days, prior infection with a carbapenem-resistant organism, and receipt of ventilatory support (c-statistic = 0.81). Risk factors for ColR-KP specifically were neurologic disease, residence in a skilled nursing facility prior to admission, receipt of carbapenems in the last 90 days, receipt of an anti-MRSA antimicrobial in the last 90 days, and prior infection with a carbapenem-resistant organism (c-statistic = 0.89). A scoring system derived from these models can be applied by humans to guide empiric antimicrobial therapy, and outperformed use of a standard hospital antibiogram in predicting infections with ColR-GNR and ColR-KP.

Keywords: Antimicrobial resistance, clinical decision making, antimicrobial testing, antimicrobial stewardship, colistin, Gram-negative rods

Introduction

The rising prevalence of infection caused by multi-drug resistant organisms (MDROs) is a worldwide problem with increasing cost and associated morbidity and mortality.[2] In the US, there are currently approximately 2 million annual cases of infections due to MDROs, with ~23,000 attributable deaths and $50 million in directly attributable costs.[1] Initial antibiotic selection remains a challenge. Delayed start of microbiologically active antibiotic therapy has been shown to increase mortality and hospital length of stay,[8,9] while overuse of broad-spectrum antibiotics has been linked with increased prevalence of MDROs.[15-19]

Colistin (polymyxin E) has been considered an antibiotic of last resort for MDR Gram-negative bacteria, due to neurotoxicity and nephrotoxicity, but it has become an increasingly important therapy when MDR pathogens are suspected, and is at times the sole antimicrobial with activity against these organisms.[38] Early, appropriate treatment of patients with colistin-resistant GNRs (ColR-GNRs) and colistin-resistant *K. pneumoniae* (ColR-KP) has been associated with reduced mortality.[39-41] The prevalence of colistin resistance among Gram-negative rods (GNRs) has been increasing over the past two decades, particularly among isolates of *Klebsiella pneumoniae,*[38,40,42-46] limiting the potential utility of colistin. Infection with ColR-GNR is associated with higher mortality than colistin-susceptible isolates,[39,40,47-50] making rapid identification of resistant important. However, early identification of ColR-GNR is challenging.

Prior literature has identified multiple risk factors for colistin resistance in GNRs, including recent prior hospitalization,[47,51,52] prior carbapenem

resistance,[40,43-45,51,53] prior treatment with colistin,[48,51,53,54] exposure to chlorhexidine,[55] and patients with multiple comorbidities,[51,52] increasing age, male sex, length of hospitalization, and presence of indwelling urinary catheters.[52] Other risk factors for development of MDROs in general included prior residence in a nursing home, hemodialysis, ICU admission,[34] presence of medical comorbidity,[49,56] prior beta-lactam usage, and invasive surgery.[56]

We hypothesized that a large, adequately powered study would provide sufficient observations to identify easily obtainable clinical factors that could serve as prediction tool for identifying patients at high risk for acquiring colistin resistant organisms, specifically ColR-KP.

Methods

We conducted a retrospective, study of all patients with positive cultures from any source over a six-year period to develop a comprehensive model for risk of infection or colonization with ColR-GNRs, with a specific focus on ColR-KP. The study was performed at two hospitals in metropolitan Los Angeles, California. Ronald Reagan UCLA Medical Center is a 520-bed tertiary care center with five adult intensive care units totaling 109 beds, Santa Monica-UCLA Medical Center has 266 beds total with 22 mixed intensive care beds in a single unit. Both are part of UCLA Health and serve patients with solid organ and bone marrow transplants, cancer, and various medical and surgical conditions. The Integrated Clinical and Research Data Repository (xDR) serves as a warehouse for all clinical data in the UCLA system since the implementation of electronic

health records in 2006. The dataset contained information from all admissions with start dates from January 2011 through November 2016 to either hospital for patients ≥18 years of age and at least one positive culture from any source (blood, urine, sputum, wound cultures, or other fluids).

Since the endpoint of this analysis was prediction of development of the first colistin resistant isolate, once a patient had a culture growing a ColR-GNR organism (defined as colistin MIC >2μg/mL), all cultures from that patient occurring at a later time than the original culture were removed from the dataset. Some isolates demonstrate intrinsic resistance to colistin namely *Burkholderia, Morganella, Proteus, Providencia,* and *Serratia spp.* With the exception of *Burkholderia* (of which there were only 16 isolates, or 0.05% of the total number), these species are typically sensitive to first-line antibiotics, do not usually acquire high-level resistance, and can be treated with standard therapy. In contrast, species with acquired colistin resistance usually do so as the end stage of a process of sequentially accumulating resistance mechanisms to other antibiotics, which makes them uniquely difficult to treat. Additionally, organisms demonstrating intrinsic resistance comprised 4,199 isolates, compared to only 128 with acquired resistance, and including them in the model would generate a model that was overly weighted toward the prediction of culture recovery intrinsically resistant organisms, which do not require non-standard therapy. Therefore, in order to focus on the clinically relevant event of transition from colistin susceptibility to resistance, isolates with intrinsic colistin resistance were excluded from the analysis.

Routine susceptibility testing was performed by the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method (BMD), using panels prepared in-house. Only data from 2011 and onwards were used in this study, as routine colistin testing was not performed prior to 2011. All antimicrobial susceptibility data were interpreted using CLSI breakpoints current to the year of testing. Because no CLSI breakpoints exist for the Enterobacteriaceae and colistin, the EUCAST breakpoint of ≤2 ug/mL to define susceptible and >2 ug/mL to define resistance was applied.

Predictor variables were chosen on the basis of prior studies, as well as those with biologic plausibility that were readily obtained from the medical record. Risk factors were identified in the literature through a partially structured search of PubMed and Google Scholar. For PubMed, the initial search used the phrase: (colistin) AND (resist* OR non-suscept* OR suscept* OR nonsuscept* OR sensiti* OR non-sensiti* OR nonsensiti*) AND (risk OR predict* OR protec*). For Google Scholar, the initial search used the phrase: colistin (resist* | non-suscept* | nonsuscept* | suscept* | sensiti* | non-sensiti* | nonsensiti*) (risk factors | predict* | protect*). Once initial articles were identified, the references cited in those articles were also explored iteratively.

Data collected for each patient included admission hospital, days since admission, location prior to admission (home vs. long-term care facility or other hospital), demographic information, comorbidities (grouped into categories based on Elixhauser score designations),[57] laboratory results from the date of the culture, vital signs on the date the culture was collected (maximum temperature,

heart rate, and respiratory rate, and minimum blood pressure), vital signs from initial hospital presentation, oxygen/ventilation method, presence of a tracheostomy, presence of urinary catheter, administration of antibiotics and other selected medications (vasopressors, probiotics, blood products, immunosuppressants, and acid suppressants), culture source, and prior culture positivity for carbapenem-resistant GNRs. Administration of antibiotics and the medications listed above was coded as the number of days since last receipt of the medication, Winsorized to a maximum value of 100 (received within 24 hours of the time of culture = 0, never received was coded as 100 days since receipt). The variable “anti-pseudomonal carbapenem” refers to receipt of meropenem, imipenem, or doripenem. “Anti-MRSA” agents refers to vancomycin, linezolid, and daptomycin, as these were used at our institution in cases of suspected hospital-acquired MRSA. Receipt of colistin was by any route, including intravenous or inhaled. An infection was coded as “hospital acquired” if the culture was submitted ot the laboratory >48 hours after the time of first presentation to the hospital.

The Elixhauser category of neurologic disease includes cerebral degeneration, movement disorders, degenerating neuropathies, seizure disorders, and anoxic brain injury.[57] The construct of advanced ventilatory support includes patients receiving either non-invasive or invasive mechanical ventilation.

In cases where laboratory tests were not performed before cultures were sent (typically at the beginning of a patient’s admission), the first set of laboratory

results were used for that patient, provided they were performed on specimens collected within 24 hours of culture positivity. For laboratory tests not typically performed daily (e.g., liver function tests, measures of coagulation, and protein/prealbumin), the most recent result within a 48-hour period prior to culture positivity was used.

Statistical Analysis

Two separate analyses were performed, one comparing all ColS-GNRs against all ColR-GNRs, and one comparing only colistin-susceptible KP (ColS-KP) against ColR-KP. These two analyses were chosen to aid decision at two separate time points, the first when only Gram stain results are available without any bacterial species information, and the second when organism identification was performed, but prior to reporting of antimicrobial susceptibility results. The measured variables in each case were compared between the cases and controls by a two-sided Mann-Whitney U test, Student's t-test, or chi-squared test, as appropriate. In each case, after bivariate associations were examined, variables with $p<0.10$ or strong biologic plausibility were included in a stepwise forward model selection procedure to create a logistic regression model for each case/control pair. Only complete cases were included in model selection. Model discrimination was assessed with area under the receiver operating characteristic curve (c-statistic), and models were compared by chi-squared test if they were nested, or Akaike information criterion if they were not.

The steps of the model selection strategy are detailed in Appendix A. In each case, the predictor variables were divided into several categories, comprising medical comorbidities, demographics (age, gender, race, location prior to admission, and social history), laboratory variables, indwelling devices, and received medications. Vital signs as a group lacked sufficient explanatory power to be included in the model. Model selection occurred in stages, with each stage involving either the introduction of a new category of predictor, or the combination of a new category with prior models. At each stage, candidate variables from the chosen new category (defined as those with $p < 0.05$ on bivariate analysis or those with $p < 0.10$ with support from prior literature) were added to an initial model, and those that became non-significant in the multivariate model were dropped. Next, variables were iteratively dropped in a backwards selection process until parsimony was achieved. A parsimonious model was defined as the model with the smallest set of predictors in which dropping additional predictors resulted in a substantial drop in AUROC. A substantial drop in AUROC was defined as a decrease of at least 0.02, and a decrease that was larger by a factor of two than the decrease in AUROC with dropping the prior, less explanatory variable. In situations with two highly correlated variables that related to closely related constructs (for example, whether a patient was currently ventilated and whether they were ventilated at any point during the index hospitalization), the variable with less explanatory power was dropped, as measured by change in AUROC. The exceptions to the above process were some laboratory values, as there were a large number of

laboratory values that were significant at $p < 0.05$ on bivariate analysis despite not having a clinically significant difference between the resistant and non-resistant groups. In these cases, the laboratory values with $p < 0.05$ were added individually to the final model to assess if they contributed significantly to the explanatory power (as defined by AUROC increase of 0.02); none of them did, and none were included.

For ColR-GNR, model selection began with the list of relevant medical comorbidities. Once this list was pared to a parsimonious model, demographic information was added and the model was pared again (Table A-1). Next, a model was constructed using only laboratory variables and, once pared, this model was combined with indwelling devices (Table A-2). These two models were combined together and pared again (Table A-3). Finally, a model was constructed using recently administered medications, and this was pared and combined with the previous predictors (Table A-4). A similar process was undertaken for ColR-KP, with the exception of a step for indwelling devices, as these did not notably improve the model when combined with other predictors (Tables A-6, A-7, and A-8).

As a sensitivity test, analyses were re-run defining colistin resistance in *Pseudomonas aeruginosa* as MIC >4μg/ mL (versus >2 ug/mL). All analyses were performed using the Stata statistical software package, version 14.2.[58]

Results

The overall dataset included 28,512 GNR isolates from 12,388 patients,

128 (0.45%) of which were ColR. 4,557 *K. pneumoniae* isolates were in the dataset, 68 (1.49%) of which were ColR. Since only complete cases were analyzed for the multivariate model, the final model for all GNRs comprised 15,372 cultures, 80 (0.52%) of which were ColR-GNR, and the final model for *Klebsiella* comprised 2,234 cultures, 34 (1.46%) of which were ColR-KP. Rates of development of ColR showed an upwards trend for both GNR and KP over the study period (Figure 3-1). Among ColR organisms, *Klebsiella* and *Acinetobacter* were overrepresented compared to colistin-susceptible organisms, while *Escherichia* and *Pseudomonas* spp. were underrepresented (Table 3-1). Among both all GNR and *Klebsiella pneumoniae*, respiratory source for the culture was predictive of ColR (Table 3-2).

Bivariate Analyses

Selected bivariate associations are reported in Table 3-3. Risk factors were similar for all GNRs and for *K. pneumoniae*, although p-values were generally smaller for GNRs due to the larger sample size. Consistent with prior literature, risk factors included admission from a nursing home, location in an ICU,[34] comorbidity (as measured by the Elixhauser score),[49,52,56] prior culture positive for a carbapenem resistant organism,[40,43-45,51,53] and prior treatment with colistin.[48,51,53,54] Increasing age was associated with ColR-KP, but not ColR-GNR. The most prominent comorbidity associated with ColR was the neurologic disease category of the Elixhauser score. Several measures of chronic or acute respiratory failure were predictive of ColR, including whether the patient was

currently receiving advanced ventilatory support, whether the patient had been on a ventilator during that hospitalization, and whether the patient had a tracheostomy at the time of culture or the time of admission. Laboratory values associated with ColR were higher neutrophil, eosinophil, and basophil counts, lower hemoglobin/hematocrit, and higher blood urea nitrogen (BUN) and alkaline phosphatase. Receipt of the following classes of drugs on the day of culture were associated with ColR-GNR (and occasionally ColR-KP, see Table 3-3): probiotics, drugs to raise blood pressure, blood products, hematopoetic agents, inhaled bronchodilators, and gastric acid suppressants. While receipt of specific antibiotics on the day of culture was associated with ColR, this relationship was better described by time since last receipt of an antibiotic. Shorter time since receipt of the following antibiotics was associated with ColR-GNR (and occasionally ColR-KP, see Table 3-3): anti-pseudomonal carbapenems, ertapenem, penicillins, anti-MRSA agents, and colistin. Of note, steroids, chemotherapy, and immunosuppressants were not associated with increased risk for ColR infections.

Multivariate Analyses

Many of the variables that were significant on bivariate analysis were strongly co-linear, and thus were categorized into our model as three major constructs representing chronic illness, antibiotic exposure, and acute illness. To facilitate model interpretability, the variables representing days since receipt of medications were dichotomized to receipt within the prior 90 days vs. not; this did

not significantly affect model fit.

For the model predicting ColR-GNR, the predictors in the final model were presence of neurologic disease (as defined by the Elixhauser score), admission from a long-term care facility, prior infection with a carbapenem-resistant infection, receipt of an anti-pseudomonal carbapenem in the prior 90 days, and receipt of advanced respiratory support at the time of culture (Table 3-4a). The first three of these variables best represented the construct of chronic illness, while the last two represented antibiotic exposure and acute illness, respectively; this model had a c-statistic of 0.81.

For the model predicting ColR-KP, the predictors in the final model were similar: presence of neurologic disease (as defined by the Elixhauser score), admission from a long-term care facility, prior infection with a carbapenem-resistant organism, receipt of an anti-pseudomonal carbapenem in the prior 90 days, and receipt of an anti-MRSA agent in the prior 90 days; this model had a c-statistic of 0.89 (Table 3-4b).

Treating each multivariate model as a score with one point assigned for each of the five items in the model, we created a potentially user-friendly tool to predict the probability of ColR in both situations. Figures 3-2 and 3-3 show the positive predictive value at each score total for GNR and KP, respectively, and demonstrate that higher score is associated with higher likelihood of Col-R with scores of >3 representing 3.5% risk of ColR-GRN and 9.6% for ColR-KP. Tables 3-5 and 3-6 show the fraction of GNR and *K. Pneumoniae* isolates, respectively, with each score, and the positive predictive value for colistin resistance at each

score. Only 79 GNR isolates had an associated score of 5, 2 of which were ColR-GNR. Similarly, only 8 *K. Pneumoniae* isolates had a score of 5, 3 of which were ColR-KP. Due to the small sample size at this score and the unusual rates observed in these small samples, in both cases the scores of 4 and 5 were combined into a single estimate for the figure and final scoring system.

Alternate scoring systems were tested for each model, with separate models assigning scoring weights in proportion to the model coefficients and in proportion to the change in odds ratios. In each case the range of predicted probabilities of resistance was similar between the upper and lower bounds of the score, but there was more granular resolution of those probabilities as a result of a larger number of possible score totals. A flat scoring system (one point per factor) was ultimately chosen for ease of interpretability by providers.

Changing the breakpoint for resistance for *P. aeruginosa* to MIC >4μg/ mL did not significantly change any of the results.

Discussion

Infection with colistin-resistant organisms is associated with substantially increased risk for mortality, and options for treatment are limited.[39-41,47-50] Prior studies have typically been relatively small or limited in scope, either following a relatively small number of patients,[31,32,34,35,39,40,47,48,54,59] or focusing on a single organism,[46,51,52,56] and none have resulted in a clinically meaningful prediction tool. Our score can be calculated by humans at the time of decision-making and potentially more accurately reflects a patient's risk for ColR organisms than a

hospital-wide or unit-specific antibiogram, which can only provide a flat percent expected susceptibility for a given organism, and is not useful for management of rare events; additionally, most hospital labs do not routinely test for colistin, and it is rarely in a hospitals antibiogram. All information used in the models was extracted directly from the medical record without any direct examination of individual patient records, allowing this score to potentially be calculated automatically.

Our bivariate analysis is largely in line with prior similar studies, demonstrating the association with prior infections with carbapenem-resistant organisms,[40,43-45,51,53] treatment with colistin,[48,51,53,54] various medical comorbidities,[49,50,52,56] increasing age, male sex, length of stay, presence of indwelling urinary catheters,[52] prior residence in a nursing home, and ICU admission.[34] While other models have focused on prior colistin exposure as a risk factor,[51,53,54] our multivariate models suggest that exposure to other antibiotics (carbapenems and anti-MRSA agents) may serve as better markers for disease risk. While it is improbable that exposure to these medications mechanistically leads to development of ColR, carbapenem receipt likely proxies recent infection with MDR GNRs, while anti-MRSA receipt proxies recent concern for sepsis, as nearly all patients with suspicion for sepsis receive at least one dose of vancomycin at our institutions. The conceptual model described in Chapter 2 suggests that acute illness does not play a large role in determining risk for recovery of a non-susceptible isolate on culture, and that the majority of risk occurs as a result of chronic illness and recent exposure to antibiotics. This

analysis supports that conclusion in several ways. First, vital signs have limited predictive power, and while some variables related to blood pressure are significant on bivariate analysis (Table 3-3), none were included in the final model. Secondly, while laboratory values individually have predictive power on bivariate analysis (Table 3-3), all except for hemoglobin (and eosinophil count, for ColR-GNR) drop out when added to prior variables in the analysis (Tables A-2 and A-7). The only laboratory value with substantial predictive power is hemoglobin (which is not included in the final models); low hemoglobin in this context is likely more related to chronic anemia than acute blood loss. In contrast, variables associated with chronic illness feature prominently in the models, most notably chronic neurologic disease and residence in a facility prior to admission (Tables A-1, A-3, A-4, A-6, A-7, and A-8). Additionally, recent antibiotic exposure figures heavily into both models (Tables A-4 and A-8).

Our score for predicting ColR-GNR is of limited utility, given that the predicted probability never exceeds 4%, but it is useful for ruling out ColR-GNR at low scores. The model for predicting ColR-KP is significantly more useful, as a score >3 indicates a nearly 10% chance of ColR-KP, at which point colistin therapy is likely risky to use as a sole therapy. Since the score is substantially more useful after species identification, it is best paired with tools that allow for early identification, such as matrix-assisted laser desorption ionization-time of flight (MALDI-TOF), or other rapid identification technologies.

Our study has limitations. It examines patients from only two hospitals within a single hospital system. The final number of ColR cases is moderate, and

approximately 50% could not be included in the final analysis due to a lack of complete data across the relevant domains. Additionally, we only had access to data from inpatient hospitalizations within our hospital system, potentially excluding relevant information from outpatient encounters or treatment at other facilities. These limitations reflect the real-world data that is available at the time of decision-making, or for eventual integration of a similar score into an electronic health record. However, it is the largest investigation to date in terms of subject number and spans a period of six years, allowing us to examine far more potential explanatory variables than prior investigations of risk factors for development of ColR-GNR or ColR-KP. By performing a cohort study of patients with positive cultures, we eliminate potential selection bias in choosing controls and strengthen the validity of observed associations.[60]

While this model and scoring system may improve initial antibiotic therapy choice for patients with suspected ColR infections, the overall outcome is rare, and empiric treatment with the higher-intensity regimens required for ColR organisms may not always be warranted. A low score effectively rules out ColR organisms, and may be helpful in allowing less intensive treatment regimens even in cases that are otherwise higher risk. In particular, while awaiting the laboratory to perform colistin susceptibility testing, which may take days to weeks to result, due to limited availability of tests for colistin.

Our study demonstrates the potential to harness currently available information from an existing electronic medical record to better inform clinical decision-makers. Our simplified scoring system clearly outperformed the

traditional antibiogram approach of offering a single hospital-wide percentage rate of susceptibility. In the current era of data intensive medical care, we should harness all available information to better manage our patients. Further research will focus on validating this score in other populations, with other antibiotics, other pathogens, and analysis of cost-benefit thresholds for initiating specific antibiotic regimens in cases of uncertainty.

Figure 3-1: Rates of development of colistin resistance by year for *K. pneumoniae* and all Gram-negative rods, excluding isolates with intrinsic colistin resistance.

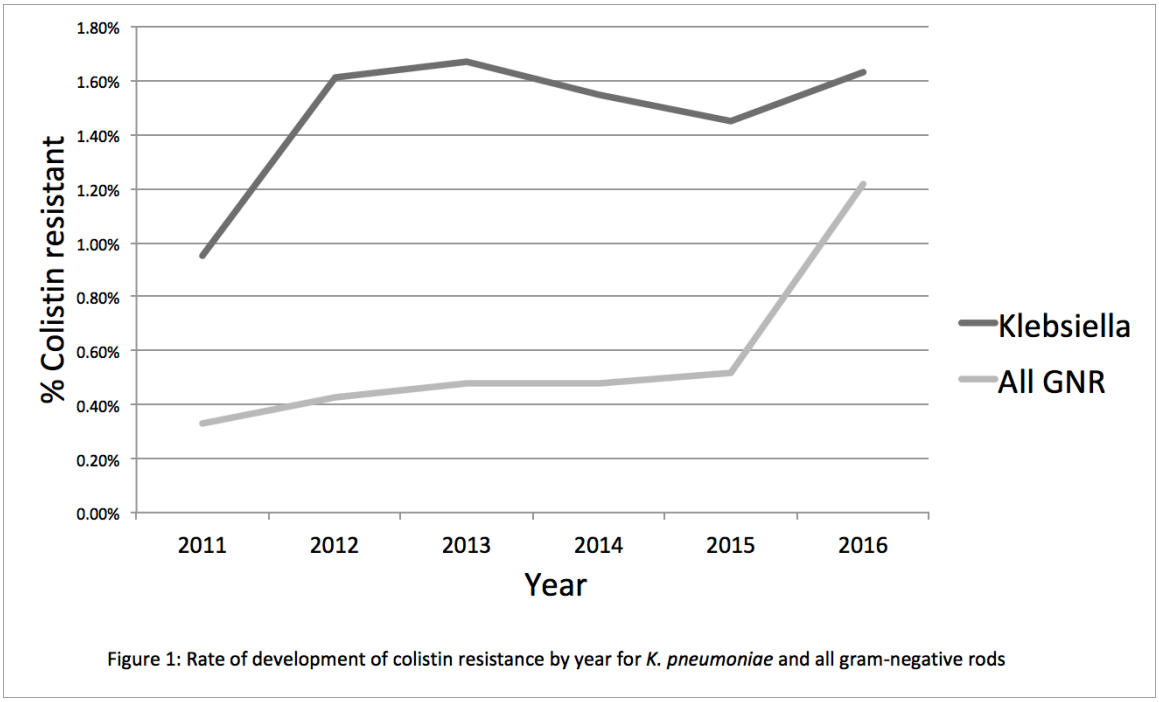


Figure 1: Rate of development of colistin resistance by year for *K. pneumoniae* and all gram-negative rods

Figure 3-2: Positive predictive value for colistin resistance at each score value for Gram-negative rods

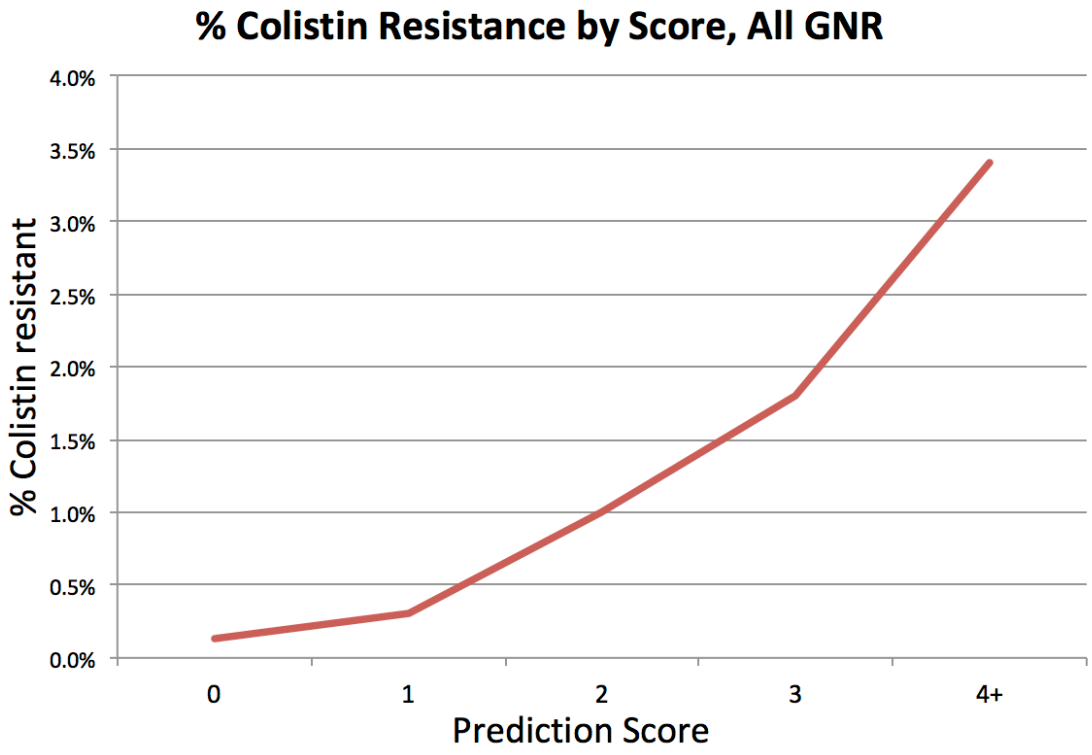


Figure 2: Positive predictive value for colistin resistance at each score for gram negative rods

Figure 3-3: Positive predictive value for colistin resistance at each score value for *K. pneumoniae*

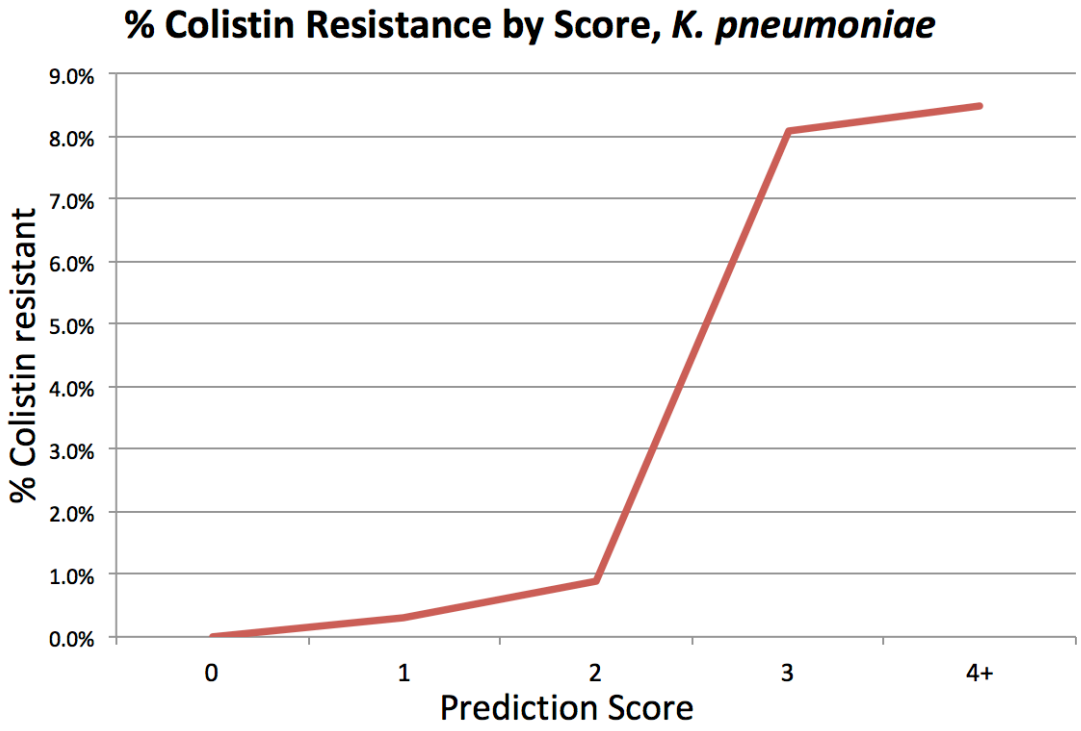


Figure 3: Positive predictive value for colistin resistance at each score for *K. pneumoniae*

Table 3-1: Distribution of organisms for ColS and ColR cultures ($p < 0.001$ for X^2 test) (ColR defined as MIC > 2ug/mL)

organism	Col-S	Col-R
Acinetobacter	2.4%	11.1%
Enterobacter	8.5%	6.2%
Escherichia	37.6%	0.4%
Klebsiella	16.0%	68.4%
Pseudomonas	22.3%	7.6%
Stenotrophomonas	3.7%	2.7%
Other	9.5%	3.6%

Table 3-2: Distribution of culture source for ColS and ColR cultures for both all GNR and *Klebsiella*. ($p < 0.001$ for X^2 for GNR, $p = 0.004$ for KP)

Specimen	ColS-GNR	ColR-GNR	ColS-KP	ColR-KP
Blood	12.0%	12.0%	16.6%	17.6%
Urine	40.0%	15.6%	42.0%	17.6%
Respiratory	28.5%	50.7%	23.4%	40.9%
External	6.9%	8.4%	5.6%	9.4%
Other	12.7%	13.3%	12.4%	14.5%

Table 3-3: Selected bivariate associations

	Col-S GNR	Col-R GNR	p-value	Col-S KP	Col-R KP	p-value
n =	28512	128		4557	68	
Age	63.1(19.3)	65.4(18.5)	0.166	62.7(18.4)	69.1(16.9)	0.004
Male Sex	47.4%	57%	0.03	49.7%	58.8%	0.134
Race			0.08			0.054
White	52.3%	51.6%		49.7%	45.6%	
Asian	8.8%	9.4%		9.8%	7.4%	
Black	10.9%	17.2%		12.0%	23.5%	
Latino	21.5%	14.1%		22.4%	16.2%	
Other	6.4%	7.8%		6.1%	7.4%	
BMI	25.8(6.7)	25.6(7.4)	0.946	26.4(7.4)	25.5(8.7)	0.564
Admitted From Healthcare Facility	14.3%	45.7%	<0.001	13.2%	55.9%	<0.001
Hospital (RRMC vs. SMH)	65.7%	56.1%	0.198	64%	53.8%	0.283
Log Days To Culture	0.69[-1.35,2.31]	1.57[-0.44,3]	<0.001	0.86[-1.27,2.38]	1.06[-0.77,2.82]	0.029
Hospital Acquired	0.463	0.516	0.237	0.487	0.515	0.647
In ICU At The Time Of Culture	20.3%	33.6%	<0.001	21.5%	32.4%	0.014
Any ICU Stay During Index Hosp.	40.3%	61.2%	<0.001	43.1%	68.3%	<0.001
Current Isolate Is Carbapenem Resistant	7.8%	71.1%	<0.001	6.3%	88.2%	<0.001
Prior Isolation Of Carbapenem-Resistant GNR	13.2%	47.7%	<0.001	12.7%	57.4%	<0.001
Presence of Indwelling Urinary Catheter	43.8%	76%	0.002	44%	75%	0.01
Ventilated During Index Hosp.	32.4%	65.1%	<0.001	33.4%	68.3%	<0.001
Tracheostomy Present On Day Of Culture	12.1%	30.2%	<0.001	8.5%	24.4%	<0.001
Tracheostomy Present On Admission	5%	16.3%	<0.001	3.3%	19.5%	<0.001
Advanced Ventilation On Day Of Culture	24%	51.2%	<0.001	25.1%	51.2%	<0.001
Elixhauser Score	16[7,27]	21[11,28]	0.005	19[9,29]	21.5[11,31]	0.021
Congestive Heart Failure	20.5%	18%	0.477	20.8%	20.6%	0.969
Arrhythmia	42.7%	56.3%	0.002	43.2%	63.2%	<0.001
Neurologic Disease	29.3%	56.3%	<0.001	29.8%	64.7%	<0.001
Chronic Pulmonary Disease	25.4%	29.7%	0.27	24%	27.9%	0.449
Liver Disease	26.5%	25%	0.704	33%	29.4%	0.527
Lymphoma	4.4%	4.7%	0.862	3.8%	2.9%	0.726
Metastatic Cancer	10.6%	5.5%	0.06	11.3%	5.9%	0.161

Non-Metastatic Cancer	23.4%	12.5%	0.004	26.6%	13.2%	0.013
Weight Loss	19.9%	32%	<0.001	22.3%	35.3%	0.011
Electrolyte Disorder	61.6%	72.7%	0.011	66.6%	76.5%	0.088
Deficiency Anemia	13.2%	14.1%	0.777	14.5%	14.7%	0.963
Drug Abuse	7.2%	5.5%	0.448	8%	4.4%	0.274
Solid Organ Transplant	19.1%	21.1%	0.559	20.6%	16.2%	0.367
Bone Marrow Transplant	1.6%	1.6%	0.991	1.3%	0%	0.345
Renal Failure	15.3%	24.2%	0.005	16.8%	29.4%	0.006
Cystic fibrosis	1.9%	6.3%	<0.001	0%	0%	0.863
HIV	0.8%	0.8%	0.992	0.5%	1.5%	0.292
Alcohol User	22.2%	15.9%	0.154	22.5%	21.4%	0.868
Tobacco User	5.6%	5.5%	0.972	5.5%	9.4%	0.347
Vital Signs On Day Of Culture						
Maximum Temperature	99.7(1.6)	99.5(1.8)	0.292	99.7(1.8)	99.6(2.3)	0.774
Maximum Pulse	104.3(23)	108.6(21.3)	0.078	105.4(23.5)	111.5(24.3)	0.089
Maximum Respiratory Rate	27.4(9.8)	28.7(8.8)	0.221	27.4(9.7)	28.8(8.4)	0.373
Minimum SBP	101.2(21.7)	93.7(21)	<0.001	100.1(22)	92.3(24.3)	0.01
Minimum DBP	58.2(12.3)	54.6(10.6)	0.006	57.7(12.3)	54.5(12.8)	0.073
Minimum MAP	72.4(14.3)	67.6(13.4)	0.001	71.8(14.3)	67.1(16)	0.022
Septic Shock	20.6%	31.3%	0.003	22.3%	32.4%	0.047
Hypotensive	21.2%	32%	0.001	22.9%	32.4%	0.034
Labs On Day Of Culture						
WBC	12.4[8.6,17.4]	14.3[9.8,20.1]	0.034	12.3[8.3,17.5]	14.7[9.8,20.1]	0.008
Hemoglobin	9.8[8.5,11.3]	9.2[8,10.1]	<0.001	9.6[8.4,11.1]	9.3[8.2,10.2]	0.002
Hematocrit	30.1[26.3,34.6]	28.2[25.2,31.8]	<0.001	29.5[25.7,33.9]	28.5[25.4,31.8]	0.009
Platelets	201[124,288]	215[123,317]	0.31	190[106,273]	209[130,297]	0.349
Sodium	137.3(5.5)	137.6(5.9)	0.55	137.2(5.6)	138.2(6.7)	0.159
Potassium	4.1(0.6)	4.1(0.7)	0.276	4.1(0.6)	4.1(0.7)	0.915
Chloride	102.4(6.5)	101.8(7.2)	0.205	102.7(6.7)	102.7(8.7)	0.948
Bicarbonate	24.5(4.8)	25.2(5.4)	0.112	23.7(4.7)	24(4.5)	0.612
Anion Gap	10.4(4)	10.7(5.2)	0.347	10.8(4.3)	11.5(5.6)	0.162
Creatinine	1.4(1.3)	1.6(1.4)	0.048	1.4(1.3)	1.7(1.4)	0.042
BUN	28.4(22.8)	36.6(26.3)	<0.001	29.5(23.1)	40.5(27.2)	<0.001
GFR	71[39,100]	61[31,100]	0.081	67[37,100]	62[31.5,100]	0.069
Glucose	135.3(57.1)	139.5(61)	0.433	137.8(60.9)	141.5(69)	0.674
Magnesium	1.7(0.3)	1.7(0.3)	0.399	1.7(0.3)	1.7(0.3)	0.859
Calcium	8.6(0.9)	8.7(1)	0.119	8.5(0.9)	8.6(1)	0.427
Phosphorus	3.3(1.2)	3.4(1.3)	0.171	3.3(1.2)	3.5(1.2)	0.187
AST	69.8(363.5)	51.6(97.6)	0.607	76.8(336.1)	65.6(128.6)	0.801
ALT	52(187.7)	47.7(87.7)	0.814	58.6(178)	59.4(109.2)	0.983

ALK	149.9(168)	217.5(361.3)	<0.001	157.3(178.2)	260.7(465.2)	<0.001
aPTT	22.7(15.3)	20.9(13.5)	0.23	23.3(15.9)	22.1(13.8)	0.604
INR	1.3(0.6)	1.3(0.3)	0.434	1.4(0.7)	1.3(0.4)	0.814
Lactate	20.5(22.5)	19.6(22)	0.766	23.3(24.4)	22(24.8)	0.797
D-dimer	3021(2518)	2773(2699)	0.686	2979(2621)	2821(2474)	0.85
Prealbumin	14.1(8.1)	14.1(7.9)	0.935	13.5(8)	12.6(6.9)	0.568
Protein	6.1(1.1)	6.1(1.1)	0.784	5.9(1)	6(1.1)	0.877
Fibrinogen	327.2(180.2)	334.6(174.1)	0.79	312.5(177.3)	326(175.1)	0.711
Days Since:						
Last Antibiotic	0[0,5]	0[0,0]	0.014	0[0,14]	0[0,0]	0.004
Last Aminoglycoside	100[100,100]	100[100,100]	<0.001	100[100,100]	100[73,100]	<0.001
Last Anti-pseudomonal Carbapenem	100[100,100]	100[8,100]	<0.001	100[100,100]	100[16,100]	<0.001
Last dose of Ertapenem	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Fluoroquinolone	100[100,100]	100[29,100]	0.039	100[100,100]	100[42,100]	0.236
Last Penicillin	100[2,100]	21[0,100]	0.002	100[0.5,100]	27.5[0,100]	0.086
Last Anti-MRSA	60[0,100]	2[0,42]	<0.001	58[0,100]	1[0,49]	<0.001
Last Colistin	100[100,100]	100[63,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Aztreonam	100[100,100]	100[100,100]	0.705	100[100,100]	100[100,100]	0.876
Last Carbapenem (any)	100[100,100]	60[0,100]	<0.001	100[100,100]	100[0,100]	<0.001
Last Beta-lactam	0[0,83]	0[0,17]	0.041	3[0,100]	0[0,19]	0.011
Last Acid Suppressant	0[0,100]	0[0,0]	0.014	0[0,88.5]	0[0,0]	0.332
Last Probiotic	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Steroid	100[20,100]	100[13,100]	0.876	100[19.5,100]	100[54,100]	0.515
Last Chemotherapy	100[100,100]	100[100,100]	0.99	100[100,100]	100[100,100]	0.723
Last Immunosuppressant	100[0,100]	100[0,100]	0.582	100[0,100]	100[0,100]	0.811
Last Blood Product	100[100,100]	100[11,100]	0.002	100[40,100]	100[11,100]	0.172

Normally-distributed outcomes are reported as mean(standard deviation), non-normally-distributed outcomes are reported as median[interquartile range]. Binary outcomes are reported as percent positive.

BMI: Body Mass Index, RRMC: Ronald Reagan Medical Center, SMH: Santa Monica UCLA Hospital, ICU: Intensive Care Unit, Hosp.: Hospitalization, Advanced Ventilation: Either non-invasive mask ventilation or endotracheal intubation, WBC: White Blood Cell count, BUN: Blood Urea Nitrogen, GFR: Race-adjusted Glomerular Filtration Rate, AST: Aspartate Aminotransferase,

ALT: Alanine Aminotransferase, ALK: Alkaline Phosphatase, aPTT: Activated Prothrombin Time, INR: International Normalized Ratio, Anti-pseudomonal Carbapenem: Meropenem, Imipenem, or Doripenem

Table 3-4: Model specifications for ColR-GNR (4a) and ColR-KP (4b)

ColR-GNR	Coefficient	Standard Error	p-value
Neurologic Disease	0.53	0.24	0.026
Facility prior to admit	0.96	0.24	<0.001
Carbapenems within 90 days	0.75	0.25	0.002
Intubation or non-invasive ventilation	0.64	0.25	0.009
Prior carbapenem resistance	0.80	0.26	0.003

ColR-KP	Coefficient	Standard Error	p-value
Neurologic Disease	0.75	0.37	0.041
Facility prior to admit	1.89	0.38	<0.001
Carbapenems within 90 days	0.76	0.40	0.059
Anti-MRSA within 90 days	1.17	0.56	0.039
Prior carbapenem resistance	1.58	0.39	<0.001

Table 3-5: Percentage of ColR-GNR having each score and percentage resistant at each score

Score	Percent of total organisms with score	Resistance rate at score
0	45.2%	0.1%
1	29.9%	0.3%
2	15.2%	0.9%
3	6.4%	1.8%
4	2.7%	3.8%
5	0.6%	2.5%

Table 3-6: Percentage of ColR-KP having each score and percentage resistant at each score

Score	Percent of total organisms with score	Resistance rate at score
0	32.3%	0.0%
1	33.0%	0.3%
2	19.4%	1.4%
3	10.3%	6.4%
4	4.7%	7.6%
5	0.4%	37.5%

Chapter 4 - Risk factors for development of carbapenem resistance among gram-negative rods

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Abstract

Infections due to carbapenem-resistant gram-negative rods (CR-GNR) are increasing in frequency and result in high morbidity and mortality. Appropriate initial antibiotic therapy is necessary to reduce adverse consequences and shorten length of stay. To determine risk factors for recovery on culture of CR-GNR, cases were retrospectively analyzed at a major academic hospital system from 2011-2016. Ertapenem resistance (ER-GNR) and anti-pseudomonal (non-ertapenem) carbapenem resistance (ACR-GNR) patterns were analyzed separately. A total of 33,541 GNR isolates from 12,516 patients were analyzed, 5,443 (16.2%) of which were ER, and 3,897 (11.6%) of which were ACR. In multivariate analysis, risk factors for ER-GNR were male sex, ventilation at any point prior to culture during the index hospitalization, presence of a tracheostomy, receipt of any carbapenem in the prior 30 days, and receipt of any anti-MRSA agent in the prior 30 days; this model had a c-statistic of 0.68. Risk factors for ACR-GNR were male sex, admission from another healthcare facility, ventilation at any point prior to culture during the index hospitalization, hemoglobin <11, and receipt of any carbapenem in the prior 30 days (c-statistic of 0.75). A straightforward scoring system derived from these models can be applied by providers to guide empiric antimicrobial therapy, and outperformed use of a standard hospital antibiogram in predicting infections with ER-GNR and ACR-GNR.

Keywords: Antimicrobial resistance, clinical decision making, antimicrobial testing, antimicrobial stewardship, carbapenems, Gram-negative rods

Introduction

Rising worldwide prevalence of human infections with multi-drug resistant organisms (MDROs) is associated with increasing morbidity, mortality, and cost.[2] In the US, there are approximately 23,000 yearly attributable deaths and $50 million in yearly attributable costs from MDRO infections.[1] Appropriate initial antibiotic therapy decreases mortality and hospital length of stay,[8,9] while overuse of broad-spectrum antibiotics has been linked with increased prevalence of MDROs;[15-19] the initial choice of antibiotic remains a challenging and high-stakes decision.

Carbapenem resistance among gram-negative rods (CR-GNRs) has been increasing over the past several decades, particularly in *Enterobacteriaceae* species.[14,61-63] Infection with CR-GNR species is associated with higher mortality,[14,61,63,64] hospital costs,[14,62] and increased risk for inappropriate antibiotic therapy[22] compared to infection with carbapenem-susceptible (CS) isolates. Delayed antimicrobial therapy (DAT) of CR-GNR has been shown to directly impact patient survival, highlighting the need for rapid identification of patients at high risk for CR-GNR.

Prior literature has identified multiple risk factors for the development of CR in various GNRs, including receipt of mechanical ventilation,[14,25,34,52,64] presence of various indwelling devices,[22,52,61,64,65] more severe illness at the time of culture (ICU stay, comorbidities, or septic shock),[14,27,52,63,64] length of hospital stay or recent hospitalization,[14,22,52,65] receipt of immunosuppression,[22,27] and recent exposure to various antibiotics.[25,27,52,61,64,65] Other risk factors for

development of MDROs in general included prior residence in a nursing home, hemodialysis, ICU admission,[34] increased medical comorbidity,[49,56] prior antibiotic usage, and invasive surgery.[56]

Anti-pseudomonal carbapenems (defined as meropenem, imipenem, and doripenem) likely have a different risk factor profile from ertapenem. Several organisms (most notably *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) have intrinsic resistance to ertapenem, but not anti-pseudomonal carbapenems. As such, we performed two separate analyses, one examining ertapenem resistance (ER) and one for anti-pseudomonal carbapenem resistance (ACR), to examine the similarities and differences in risk factors for recovery of a non-susceptible isolate.

Prior studies of risk factors for CR among GNRs have largely focused on the family *Enterobacteriales* which includes many commonly treated GNRs, but excludes several clinically significant genera, including *Pseudomonas* and *Acinetobacter*. Additionally, many of these studies have been limited in scope, analyzing a small number of patients (typically in the low hundreds),[22,25,27,48,52,61,63-65] or focusing on a single organism.[25,48,52,61,65] The largest prior study of ~40,000 patients with *Enterobacteriaceae* infection (including 1,227 with CRE) used hospital administrative data, and while it had an extensive list of covariates it did not include information about non-Enterobacteriales GNRs or prior antibiotic exposure, and did not include a multivariate analysis or result in a clinical decision rule.[14] We hypothesized that a large, adequately powered study would provide sufficient observations to identify

easily obtainable clinical factors that could serve as prediction tool for identifying patients at high risk for acquiring CR-GNRs.

Methods

We conducted a retrospective study of all patients with positive cultures from any source over a six-year period to develop a comprehensive model for risk of infection or colonization with CR-GNRs, with separate analyses for ER-GNR and ACR-GNR. The study was performed at two hospitals in metropolitan Los Angeles, California. Ronald Reagan UCLA Medical Center is a 520-bed tertiary care center with five adult intensive care units totaling 109 beds, Santa Monica-UCLA Medical Center has 266 beds total with 22 mixed intensive care beds in a single unit. Both are part of UCLA Health and serve patients with solid organ and bone marrow transplants, cancer, and various medical and surgical conditions. The Integrated Clinical and Research Data Repository (xDR) serves as a warehouse for all clinical data in the UCLA system since 2006. The dataset contained information from all admissions with start dates from January 2011 through November 2016 to either hospital for patients ≥18 years of age and at least one positive culture from any source (blood, urine, sputum, wound cultures, or other fluids).

Since the endpoint of this analysis was prediction of development of the first carbapenem non-susceptible isolate, once a patient had a culture growing a CR-GNR organism, defined using Clinical and Laboratory Standards Institute (CLSI), breakpoints current to the year of testing, all cultures from that patient

occurring at a later time than the original culture were removed from the dataset.

Routine susceptibility testing was performed by the either the CLSI reference broth microdilution method (BMD), or using a Vitek 2 with BMD confirmation, using panels prepared in-house. Only data from 2011 and onwards were used in this study, as a changeover in clinical data warehousing methods corresponded to significantly more robust clinical information after that time. All antimicrobial susceptibility data were interpreted using CLSI breakpoints current to the year of testing, which have not changed since 2011. Isolates with intermediate susceptibility to either antibiotic class were categorized as resistant for the purposes of this analysis. Isolates with intrinsic resistance to the studied antibiotics were included in the analysis as resistant isolates.

Predictor variables were chosen on the basis of prior studies, as well as those with biologic plausibility that were readily obtained from the medical record. Risk factors were identified in the literature through a partially structured search of PubMed and Google Scholar. For PubMed, the initial search used the phrase: (carbapenem OR meropenem OR ertapenem OR imipenem OR doripenem) AND (resist* OR non-suscept* OR suscept* OR nonsuscept* OR sensiti* OR non-sensiti* OR nonsensiti*) AND (risk OR predict* OR protec*). For Google Scholar, the initial search used the phrase: (carbapenem | meropenem | ertapenem | imipenem | doripenem) (resist* | non-suscept* | nonsuscept* | suscept* | sensiti* | non-sensiti* | nonsensiti*) (risk factors | predict* | protect*). Once initial articles were identified, the references cited in those articles were also explored iteratively.

Data collected for each patient included admission hospital, days since admission, location prior to admission (home vs. long-term care facility or other hospital), demographic information, comorbidities (grouped into categories based on Elixhauser score designations)[57], laboratory results from the date of the culture, vital signs on the date the culture was collected (maximum temperature, heart rate, and respiratory rate, and minimum blood pressure), vital signs from initial hospital presentation, oxygen/ventilation method, presence of a tracheostomy, presence of urinary catheter, administration of antibiotics and other selected medications (vasopressors, probiotics, blood products, immunosuppressants, and acid suppressants), culture source, and prior culture positivity for carbapenem-resistant GNRs. Administration of antibiotics and the medications listed above was coded as the number of days since last receipt of the medication, Winsorized to a maximum value of 100 (received within 24 hours of the time of culture = 0, never received was coded as 100 days since receipt). “Anti-MRSA” agents refer to vancomycin, linezolid, and daptomycin, as these were used at both hospitals in cases of suspected hospital-acquired MRSA. Receipt of antibiotics were by any route, including oral, intravenous, and inhaled. An infection was coded as “hospital acquired” if the culture was submitted to the laboratory >48 hours after the time of first presentation to the hospital. The construct of advanced ventilatory support includes patients receiving either non-invasive or invasive mechanical ventilation.

In cases where laboratory tests were not performed before cultures were performed (typically at the beginning of a patient’s admission), the first set of

laboratory results were used for that patient, provided they were performed on specimens collected within 24 hours of culture positivity. For laboratory tests not typically performed daily (e.g., liver function tests, measures of coagulation, and protein/prealbumin), the most recent result within a 48-hour period prior to culture positivity was used.

To facilitate model interpretability, some linear variables were recategorized as binary variables using cutoffs. Various cutoffs were tested against each other in the final model (e.g. 30 vs. 60 vs. 90 days since receipt of last antibiotic), and the cutoff that led to the highest c-statistic was chosen for inclusion in the scoring system.

Statistical Analysis

Two separate analyses were performed, one comparing all ertapenem-susceptible GNRs (ES-GNR) against ER-GNR, and one comparing anti-pseudomonal carbapenem-susceptible GNR (ACS-GNR) against ACR-GNR. These two analyses were chosen to aid decision at the point of initial antibiotic choice, when the consequences for inappropriate antibiotic therapy are the greatest.[6,10,12,66] The measured variables in each case were compared between the cases and controls by a two-sided Mann-Whitney U test, Student's t-test, or chi-squared test, as appropriate. In each case, after bivariate associations were examined, variables with $p<0.10$ or strong biologic plausibility were included in a stepwise forward model selection procedure to create a logistic regression model for each analysis. Only complete cases were included in model selection. Model

discrimination was assessed with area under the receiver operating characteristic curve (c-statistic), and models were compared by chi-squared test if they were nested, or Akaike information criterion if they were not.

The steps of the model selection strategy are detailed in Appendix B. In each case, the predictor variables were divided into several categories, comprising medical comorbidities, demographics (age, gender, race, location prior to admission, and social history), laboratory variables, indwelling devices, and received medications. Vital signs as a group lacked sufficient explanatory power to be included in the model. Model selection occurred in stages, with each stage involving either the introduction of a new category of predictor, or the combination of a new category with prior models. At each stage, candidate variables from the chosen new category (defined as those with $p < 0.05$ on bivariate analysis or those with $p < 0.10$ with support from prior literature) were added to an initial model, and those that became non-significant in the multivariate model were dropped. Next, variables were iteratively dropped in a backwards selection process until parsimony was achieved. A parsimonious model was defined as the model with the smallest set of predictors in which dropping additional predictors resulted in a substantial drop in AUROC. A substantial drop in AUROC was defined as a decrease of at least 0.02, and a decrease that was larger by a factor of two than the decrease in AUROC with dropping the prior, less explanatory variable. In situations with two highly correlated variables that related to closely related constructs (for example, whether a patient was currently ventilated and whether they were ventilated at

any point during the index hospitalization), the variable with less explanatory power was dropped, as measured by change in AUROC. The exceptions to the above process were some laboratory values, as there were a large number of laboratory values that were significant at $p < 0.05$ on bivariate analysis despite not having a clinically significant difference between the resistant and non-resistant groups. In these cases, the laboratory values with $p < 0.05$ were added individually to the final model to assess if they contributed significantly to the explanatory power (as defined by AUROC increase of 0.02); none of them did, and none were included.

In both cases, model selection began with the list of relevant medical comorbidities. Once this list was pared to a parsimonious model, demographic information was added and the model was pared again (Tables B-1 and B-6). Next, relevant indwelling devices were added to the model and the model was pared (Tables B-2 and B-7). Then, a model was constructed using only laboratory variables and, once pared, this model was combined with the final model from the previous table (Tables B-3 and B-8). Finally, a model was constructed using recently administered medications, and this was pared and combined with the previous predictors (Tables B-4 and B-9).

All analyses were performed using the Stata statistical software package, version 14.2.[58]

Results

The complete dataset included 33,541 GNR isolates from 12,516 patients,

5,443 (16.2%) of which were ER, and 3,897 (11.6%) of which were ACR. Since only complete cases were analyzed for the multivariate model, the final model for ER comprised 14,682 cultures, 3,007 (20.5%) of which were ER-GNR, and the final model for ACR comprised 15,635 cultures, 1,961 (12.5%) of which were ACR-GNR. The majority of ER-GNR were *Pseudomonas* species, while the most common ES-GNR were *Escherichia coli* and *Klebsiella* species; the most common ACR-GNR were again *Pseudomonas* species, while the most common ACS-GNR were again *Escherichia* species (Table 4-1). Respiratory culture source was predictive of both ER-GNR and ACR-GNR, while urinary source was predictive of both ES-GNR and ACS-GNR (Table 4-2).

Bivariate Analyses

Selected bivariate associations are reported in Table 4-3. Risk factors were similar for ER-GNR and ACR-GNR. Male sex was strongly associated with both ER and ACR. The most prominent comorbidities associated with ER and ACR were the neurologic disease and weight loss categories of the Elixhauser score, as well as cystic fibrosis, although these associations were not preserved on multivariate analysis. Consistent with prior published studies,[14,25,34,52,64] several measures of chronic or acute respiratory failure were predictive of both ER and ACR, including whether the patient was currently receiving advanced ventilatory support, whether the patient had been on a ventilator during that hospitalization, and whether the patient had a tracheostomy at the time of culture or the time of admission. Longer length of stay prior to culture was positively

associated with ER and ACR. Markers of acute disease severity, such as hypotension and active septic shock, were associated more strongly with ACR than ER; prior literature has described similar findings.[14,22,52,65] Blood count values associated with ER and ACR were higher neutrophil, eosinophil, and basophil counts, lower hemoglobin/hematocrit, and lower platelets. Several other laboratory values were associated with ER and ACR, most notably higher bicarbonate, blood urea nitrogen, and alkaline phosphatase. Consistent with prior literature,[25,27,52,61,64,65] more recent receipt of any and all studied antibiotics was associated with ER and ACR, as well as more recent receipt of probiotics, acid suppressants, blood products, and chemotherapeutic agents; ER was also associated with more recent receipt of any steroid or other immunosuppressant.

Multivariate Analyses

Many of the variables that were significant on bivariate analysis were strongly co-linear, and were tested against each other in groups to determine which predictors were most representative from the various groupings of medical comorbidities, demographics, laboratory values, indwelling devices, and recently administered medications. To facilitate model interpretability, the variables representing days since receipt of medications were dichotomized to receipt within the prior 30 days vs. not; this did not significantly affect model fit. Hemoglobin was tested at multiple thresholds from 7-13g/dL; a cutoff of 11g/dL was found to have the best model discrimination.

For the model predicting ER-GNR, the predictors in the final model were

male sex, ventilation at any point prior to culture during the index hospitalization, presence of a tracheostomy, receipt of any carbapenem in the prior 30 days, and receipt of any anti-MRSA agent in the prior 30 days; this model had a c-statistic of 0.68 (Table 4-4a).

For the model predicting ACR-GNR, the predictors in the final model were somewhat overlapping: male sex, admission from another healthcare facility, ventilation at any point prior to culture during the index hospitalization, hemoglobin <11, and receipt of any carbapenem in the prior 30 days; this model had a c-statistic of 0.75 (Table 4-4b).

Treating each multivariate model as a score with one point assigned for each of the five items in the model, we created a potentially user-friendly tool to predict the probability of ER and ACR. Figures 4-1 and 4-2 show the positive predictive value at each score total for ER and ACR, respectively, and demonstrate that higher score is associated with higher likelihood of resistance. Rates of ER range from 8.7% for a score of 0 to 59.0% at a score of 5. Rates of ACR range from 1.1% at a score of 0 to 41.9% at a score of 5. Tables 4-5 and 4-6 show the fraction of GNR with each score for ertapenem and anti-pseudomonal carbapenem resistance, respectively, and the positive predictive value for resistance at each score.

Alternate scoring systems were tested for each model, with separate models assigning scoring weights in proportion to the model coefficients and in proportion to the change in odds ratios. In each case the range of predicted probabilities of resistance was similar between the upper and lower bounds of

the score, but there was more granular resolution of those probabilities as a result of a larger number of possible score totals. A flat scoring system (one point per factor) was ultimately chosen for ease of interpretability by providers.

Discussion

Infection with CR-GNR is associated with substantially increased cost and risk for mortality, and appropriate antibiotic treatment is paramount in mitigating these risks [14,22,61-64]. Our scores can be calculated by providers at the time of decision-making and potentially more accurately reflects a patient's risk for carbapenem-resistant organisms than a hospital-wide or unit-specific antibiogram, which provides a flat percent observed susceptibility for a given organism in the prior year, and is not useful for management of rare events. All information used in the models was extracted directly from the medical record without any direct examination of individual patient records, allowing this score to potentially be calculated automatically.

Our bivariate analysis is consistent with prior studies, confirming associations between CR and receipt of mechanical ventilation and presence of various indwelling devices,[14,22,25,34,52,61,64,65] more severe illness at the time of culture,[14,27,52,63,64] length of hospital stay or recent hospitalization,[14,22,52,65] and recent exposure to various antibiotics.[25,27,52,61,64,65] Several factors that featured prominently in other analyses were found not to contribute to the optimal prediction model. Length of stay, medical comorbidities, and receipt of immunosuppressive medications, while individually important, do not directly

contribute on multivariate analysis. This is most likely because they are related to a construct of chronic medical illness that is mediated through other concepts (such as frequent contact with the medical system, exposure to MDROs, and susceptibility to infection) that are better proxied by other variables.

While it is improbable that exposure to all antibiotics mechanistically leads to development of CR, some of these exposures likely proxy recent infection with MDR GNRs, while anti-MRSA receipt proxies recent concern for sepsis, as nearly all patients with suspicion for sepsis receive at least one dose of vancomycin at our institutions. The conceptual model described in Chapter 2 suggests that acute illness does not play a large role in determining risk for recovery of a non-susceptible isolate on culture, and that the majority of risk occurs as a result of chronic illness and recent exposure to antibiotics. This analysis supports that conclusion in several ways. First, vital signs have limited predictive power, and while some variables related to blood pressure are significant on bivariate analysis (Table 4-3), none were included in the final model. Secondly, while laboratory values individually have predictive power on bivariate analysis (Table 4-3), all except for hemoglobin drop out when added to prior variables in the analysis (Tables B-3 and B-8). The only laboratory value with substantial predictive power is hemoglobin (which is included in the final model for ACR-GNR); low hemoglobin in this context is likely more related to chronic anemia than acute blood loss. Variables associated with chronic illness feature prominently in the models. In both models, chronic weight loss (which is associated chronic disease and malnutrition) is a significant medical comorbidity

(Tables B-1 and B-6), although in both cases all Elixhauser categories drop out of the models when combined with demographic information and chronic indwelling devices (Tables B-2 and B-7). The final model for ER-GNR comprises markers of need for respiratory support (ventilation and tracheostomy), male gender, and recent antibiotic exposure (Table B-5); in this case the indwelling tracheostomy is most likely a consequence of chronic medical illness as opposed to acute decompensation. The final model for ACR-GNR comprises male gender, recent antibiotic exposure, anemia, transfer from another medical facility, and ventilation during the current hospital stay. While ventilation during the current hospital stay in both cases could proxy both acute and chronic illness, the majority of other risk factors in the model are more associated with chronic illness as opposed to acute decompensation.

The discrimination ability for the ER-GNR model is more limited than for the ACR-GNR model, likely because the populations susceptible to ES-GNR and ER-GNR are relatively similar. The majority of ER-GNR isolates are *P. aeruginosa*, and infection by this organism is likely driven more by random chance than is acquisition of an ACR organism. While the risk factors for ER-GNR are generally similar to those for ACR-GNR, the final model for ER-GNR risk contains variables that are more relevant to chronic respiratory failure and antibiotic exposure, which are likely indicative of risk for chronic colonization with *P. aerguinosa* and similar organisms with intrinsic resistance. The risk factors in the ACR-GNR model are similarly correlated with risk for chronic colonization, but focus more on prolonged contact with the healthcare system (admission from

another healthcare facility) and chronic disease states (best represented by anemia). The model discrimination for the ACR-GNR model is substantially better than for the ER-GNR model, indicating that the populations susceptible to ACR (vs. ACS) GNR infections differ in more identifiable ways; as such, the model is more able to rule out ACR-GNR infections at lower scores, with a <5% risk for ACR-GNR infection at scores <2.

Our study has limitations. It examines patients from only two hospitals within a single hospital system. Approximately 50% of ER- and ACR-GNR cases could not be included in the final analysis due to a lack of complete data across the relevant domains. Sensitivity analyses did not show a significant effect from missing data, although it is possible that the point estimates would have varied slightly if full data were available. Additionally, we only had access to data from inpatient hospitalizations within our hospital system, potentially excluding relevant information from outpatient encounters or treatment at other facilities. These limitations reflect the real-world data that is available at the time of decision-making, or for eventual integration of a similar score into an electronic health record. However, it is the largest investigation to date in terms of subject number and spans a period of six years, allowing us to examine far more potential explanatory variables than prior investigations of risk factors for development of ER-GNR and ACR-GRN. By performing a cohort study of patients with positive cultures, we eliminate potential selection bias in choosing controls and strengthen the validity of observed associations.[60]

While the discriminatory capacity of the ER-GNR model is limited, the ACR-GNR model can effectively rule out ACR risk (<5% chance) at scores <2, allowing reasonably confident treatment with anti-pseudomonal carbapenems as a first option without waiting for definitive carbapenem susceptibility testing, which can take up to several days.

Our study demonstrates the potential to harness currently available information from an existing electronic medical record to inform clinical decision-makers. Our simplified scoring system clearly outperformed the traditional antibiogram approach of offering a single hospital-wide percentage rate of susceptibility, by creating an individualized score than can be used and interpreted by individual clinicians without computer assistance. In the current era of data-intensive medical care, we should harness all available information to better manage our patients. Further research will focus on validating this score in other populations, and analysis of cost-benefit thresholds for initiating specific antibiotic regimens in cases of uncertainty.

Figure 4-1: Positive predictive value for ertapenem resistance at each score value for Gram-negative rods

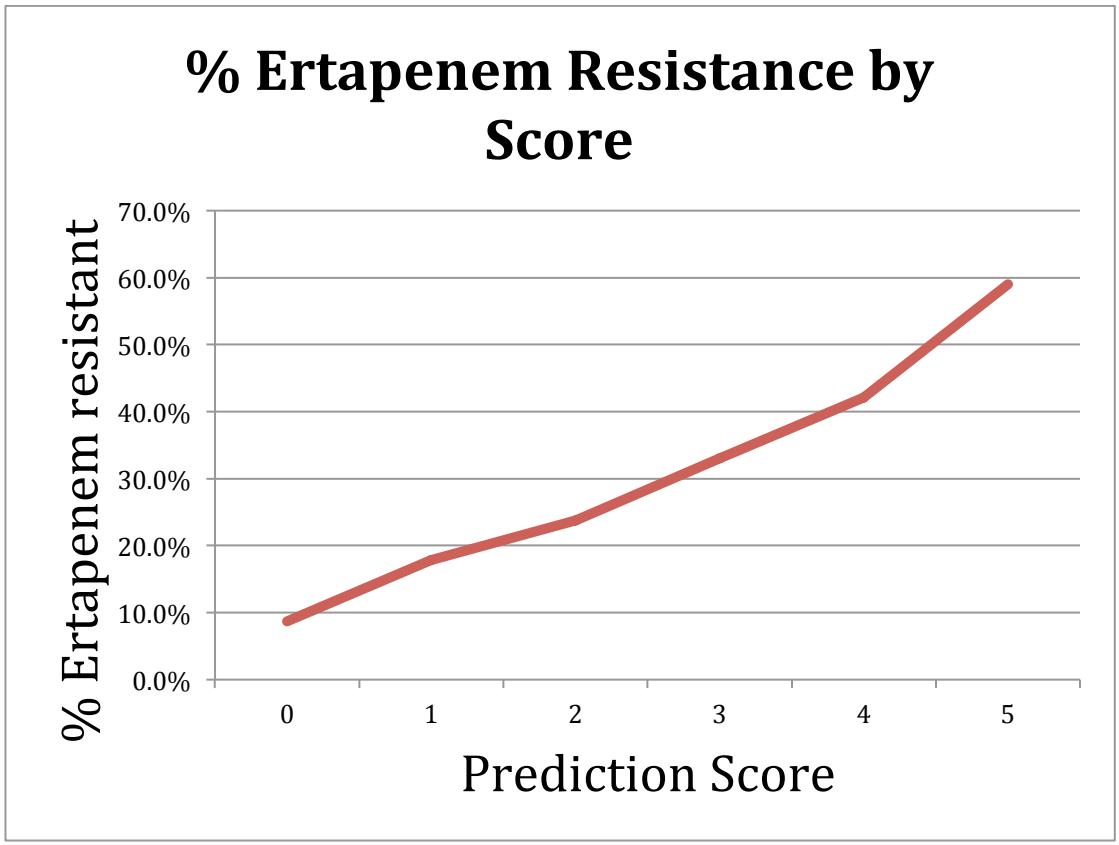

Figure 4-2: Positive predictive value for anti-pseudomonal carbapenem resistance at each score value for Gram-negative rods

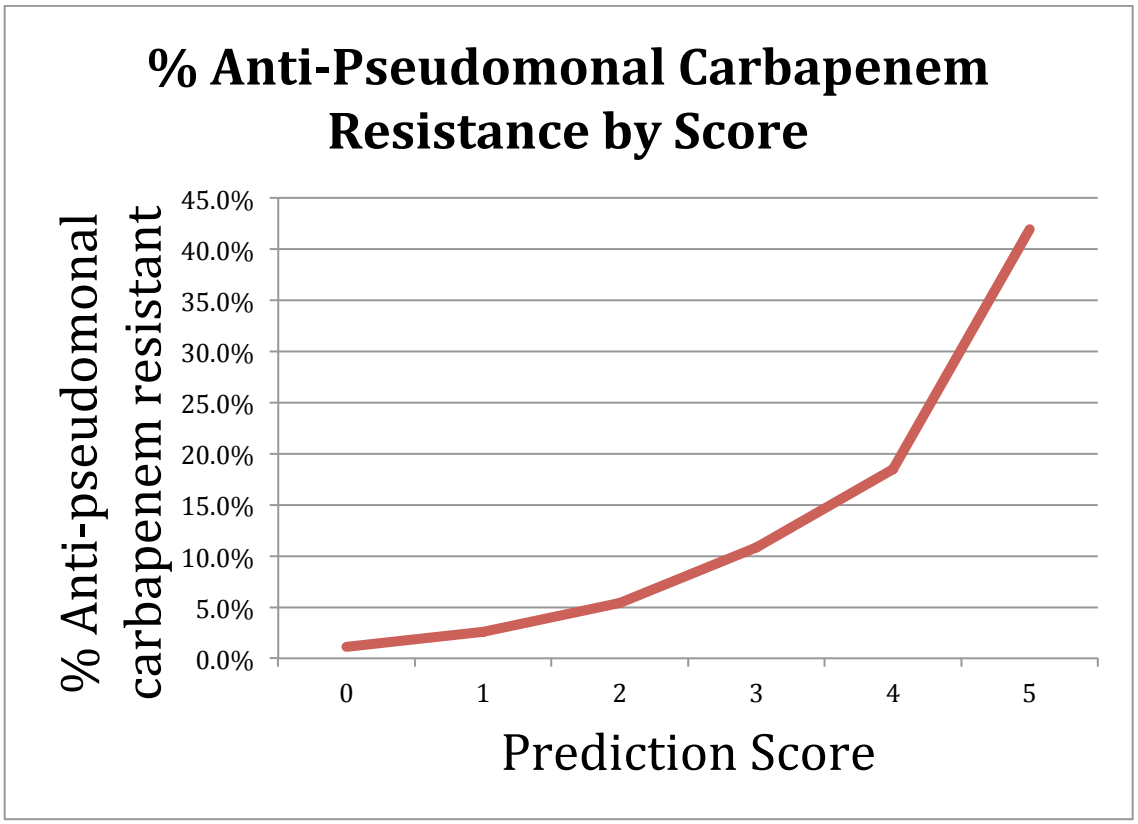

Table 4-1: Distribution of organisms for ER-GNR and ACR-GNR cultures ($p < 0.001$ for X^2 test)

Genus	ER-GNR	ACR-GNR
Acinetobacter	7.1%	10.3%
Enterobacter	2.4%	1.1%
Escherichia	1.2%	0.9%
Klebsiella	5.2%	12.1%
Pseudomonas	64.6%	46.0%
Stenotrophomonas	10.9%	27.5%
Other	8.6%	2.1%

Table 4-2: Distribution of culture source for ES-GNR, ER-GNR, ACS-GNR, and ACS-GNR ($p < 0.001$ for X^2 test for both ER and ACR)

Source	ES-GNR	ER-GNR	ACS-GNR	ACR-GNR
Blood	11.2%	7.7%	12.1%	8.4%
Urine	45.6%	18.1%	42.1%	11.2%
Respiratory	20.4%	52.0%	23.7%	61.6%
External	8.3%	9.4%	8.1%	7.9%
Other	14.5%	12.8%	14.0%	10.9%

Table 4-3: Selected bivariate associations

n =	16298	5443	p-value	29,664	1,932	p-value
Age	64.5(18.8)	63.6(18.9)	0.003	64(19.1)	63.6(18.9)	0.427
Male Sex	45.1%	56%	<0.001	46.4%	59.1%	<0.001
Race			<0.001			<0.001
White	51.1%	54.8%		52.7%	53.6%	
Asian	9.1%	7.0%		8.7%	6.8%	
Black	11.4%	13.3%		11.5%	14.2%	
Latino	21.9%	19.1%		21.0%	18.0%	
Other	6.5%	5.9%		6.2%	7.3%	
BMI	26.3(6.8)	25.6(6.8)	<0.001	26.1(6.8)	25.1(6.7)	<0.001
Admitted From Healthcare Facility	14.5%	23.1%	<0.001	14.6%	33.2%	<0.001
Hospital (RRMC vs. SMH)	65.7%	59.9%	<0.001	63.3%	53.7%	<0.001
Log Days To Culture	0.13[-1.84,1.99]	1.02[-0.97,2.51]	<0.001	0.44[-1.48,2.09]	1.6[-0.5,2.9]	<0.001
Hospital Acquired	41.2%	51.6%	<0.001	48.7%	51.5%	<0.001
In ICU At The Time Of Culture	18.5%	22.7%	<0.001	17.5%	29.1%	<0.001
Any ICU Stay During Index Hosp.	32.4%	49.1%	<0.001	36.1%	57.7%	<0.001
Presence of Indwelling Urinary Catheter	42.5%	54.4%	<0.001	43.7%	63.5%	<0.001
Ventilated During Index Hosp.	24.2%	44.9%	<0.001	28%	57.6%	<0.001
Tracheostomy Present On Day Of Culture	6.9%	21%	<0.001	9.6%	28.9%	<0.001
Tracheostomy Present On Admission	3.1%	11.4%	<0.001	4.4%	16.6%	<0.001
Advanced Ventilation On Day Of Culture	17.8%	33.7%	<0.001	20.8%	43.7%	<0.001
Elixhauser Score	14[5,25]	18[8,29]	<0.001	16[6,26]	22[12,31]	<0.001
Congestive Heart Failure	19.1%	22.8%	<0.001	19.8%	26.9%	<0.001
Arrhythmia	40%	47.5%	<0.001	41.6%	53.9%	<0.001
Valvular Disease	22.4%	26.1%	<0.001	24.3%	27.2%	0.005
Pulmonary Vascular Disease	14.6%	18.7%	<0.001	16.1%	20.3%	<0.001
Peripheral Vascular Disease	21.4%	26.6%	<0.001	23.4%	28%	<0.001
Paralysis	7.2%	9.1%	<0.001	7.8%	9.7%	0.004
Neurologic Disease	25.9%	36.9%	<0.001	28.5%	43.5%	<0.001
Chronic Pulmonary Disease	22%	29.7%	<0.001	24.7%	32.6%	<0.001
Renal Disease	31.8%	37.5%	<0.001	33.3%	40.5%	<0.001
Liver Disease	23.7%	24%	0.702	24.3%	28.1%	<0.001

Lymphoma	3.8%	5.2%	<0.001	4.1%	5.9%	<0.001
Metastatic Cancer	9.6%	10.6%	0.046	10.5%	10.4%	0.933
Non-Metastatic Cancer	22.8%	22.2%	0.340	23%	21%	0.042
Coagulopathy	24.6%	28.5%	<0.001	26%	35%	<0.001
Weight Loss	16.4%	25.1%	<0.001	18.7%	31.6%	<0.001
Electrolyte Disorder	58.2%	64.2%	<0.001	60.3%	71.5%	<0.001
Deficiency Anemia	4.7%	5.7%	0.004	5.2%	6.8%	0.002
Drug Abuse	6.6%	6.9%	0.315	6.9%	6.9%	0.97
Solid Organ Transplant	16.3%	18.2%	0.001	17%	19%	0.028
Bone Marrow Transplant	1%	1.7%	<0.001	1.3%	2.3%	<0.001
Renal Failure	13.2%	17.3%	<0.001	14.1%	19.9%	<0.001
Cystic fibrosis	0.2%	2.3%	<0.001	1%	3.6%	<0.001
HIV	0.7%	0.8%	0.757	0.7%	0.7%	0.975
Alcohol User	22.6%	20.8%	0.024	22.5%	17.7%	<0.001
Tobacco User	5.9%	6.4%	0.224	5.9%	5.5%	0.568
Vital Signs On Day Of Culture						
Maximum Temperature	99.6(1.6)	99.6(1.5)	0.514	99.7(1.6)	99.6(1.6)	0.057
Maximum Pulse	102.1(22.5)	104.5(22.6)	<0.001	103.3(22.7)	106.6(23.3)	<0.001
Maximum Respiratory Rate	26.2(9.2)	28.3(10)	<0.001	26.9(9.5)	29.5(10.2)	<0.001
Minimum SBP	103.3(21.8)	99.5(21.8)	<0.001	102(21.7)	96.9(21.7)	<0.001
Minimum DBP	59(12.4)	57.6(12.4)	<0.001	58.5(12.3)	56.5(12.7)	<0.001
Minimum MAP	73.7(14.3)	71.5(14.3)	<0.001	72.9(14.3)	69.9(14.6)	<0.001
Septic Shock	20.9%	19.6%	0.040	18.5%	24.8%	<0.001
Hypotensive	21.8%	20.3%	0.026	19.1%	25.7%	<0.001
Labs On Day Of Culture						
WBC	12.4[8.6,17.1]	13.2[9.1,18.3]	<0.001	12.4[8.6,17.2]	13.7[9.5,19]	<0.001
Hemoglobin	10.1[8.7,11.7]	9.5[8.4,10.9]	<0.001	9.9[8.7,11.5]	9.2[8.2,10.4]	<0.001
Hematocrit	30.8[26.7,35.4]	29.4[26.1,33.6]	<0.001	30.5[26.6,35]	28.7[25.4,32.4]	<0.001
Platelets	204[132,287]	217[133,313]	<0.001	205[132,290]	215[117,321]	0.032
Sodium	137.3(5.7)	137.7(5.4)	<0.001	137.3(5.5)	138.2(5.6)	<0.001
Potassium	4.1(0.6)	4.1(0.6)	0.043	4.1(0.6)	4.1(0.6)	0.069
Chloride	102.4(6.6)	102.5(6.6)	0.585	102.6(6.5)	102.5(6.9)	0.738
Bicarbonate	24.2(4.5)	25.2(5)	<0.001	24.3(4.7)	25.5(5.3)	<0.001
Anion Gap	10.7(4)	10(4)	<0.001	10.4(4)	10.1(4.2)	0.003
Creatinine	1.4(1.3)	1.4(1.4)	0.762	1.4(1.4)	1.4(1.3)	0.823
BUN	28(22.5)	30.7(25.5)	<0.001	28.3(23.1)	33.3(27)	<0.001
GFR	69[39,100]	75[39,100]	<0.001	71[39,100]	73[37,100]	0.079
Glucose	136.5(59.7)	133.6(54.4)	0.002	135.4(58.2)	134(55.5)	0.31
Magnesium	1.7(0.3)	1.7(0.3)	<0.001	1.7(0.3)	1.7(0.3)	<0.001

Calcium	8.6(0.8)	8.6(0.9)	0.235	8.6(0.8)	8.6(1)	0.327
Phosphorus	3.3(1.2)	3.3(1.2)	0.558	3.3(1.1)	3.3(1.2)	0.088
AST	68(319.3)	62.1(338.8)	0.319	64.9(320)	66.7(322.5)	0.832
ALT	49.3(144.8)	48(203.5)	0.670	49.9(170.4)	47.7(139.9)	0.637
ALK	138.5(148.1)	155.4(166.1)	<0.001	141.4(152.3)	174.8(188.6)	<0.001
aPTT	22(14.6)	22.9(15)	<0.001	22.4(14.9)	23.9(15.7)	<0.001
INR	1.3(0.6)	1.3(0.6)	0.485	1.3(0.6)	1.4(0.6)	0.072
Lactate	20.9(21.8)	18.4(19.1)	<0.001	20.9(22.8)	19(20.8)	0.008
D-dimer	3054 (2596)	2962 (2511)	0.484	3035 (2578)	3043 (2485)	0.964
Prealbumin	14.2(8.1)	14.2(7.7)	0.974	14.3(8.2)	13.7(7.6)	0.082
Protein	6.1(1)	6(1.1)	0.018	6.1(1.1)	6(1.1)	0.03
Fibrinogen	323(178.8)	338.5(187.2)	0.005	329.4(181.4)	347.1(195.8)	0.018
Days Since:						
Last Antibiotic	0[0,12]	0[0,2]	<0.001	0[0,8]	0[0,0]	<0.001
Last Aminoglycoside	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Anti-Pseudomonal Carbapenem	100[100,100]	100[100,100]	<0.001	100[100,100]	100[6,100]	<0.001
Last Ertapenem	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Carbapenem (any)	100[100,100]	100[21,100]	<0.001	100[100,100]	100[0,100]	<0.001
Last Fluoroquinolone	100[100,100]	100[97,100]	<0.001	100[100,100]	100[37,100]	<0.001
Last Penicillin	100[2,100]	100[1,100]	<0.001	100[1,100]	48[2,100]	<0.001
Last Anti-MRSA	100[1,100]	9[0,100]	<0.001	100[0,100]	4[0,72]	<0.001
Last Colistin	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Aztreonam	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Beta-lactam	1[0,100]	0[0,22]	<0.001	0[0,100]	0[0,10]	<0.001
Last Acid Suppressant	0[0,100]	0[0,100]	<0.001	0[0,100]	0[0,61]	<0.001
Last Probiotic	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Steroid	100[100,100]	100[19,100]	<0.001	100[58,100]	100[30,100]	0.074
Last Chemotherapy	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	0.003
Last Immunosuppressant	100[10,100]	100[0,100]	<0.001	100[1,100]	100[3,100]	0.368
Last Blood Product	100[100,100]	100[100,100]	<0.001	100[100,100]	100[21,100]	<0.001

Normally-distributed outcomes are reported as mean(standard deviation), non-normally-distributed outcomes are reported as median[interquartile range]. Binary outcomes are reported as percent positive.

BMI: Body Mass Index, RRMC: Ronald Reagan Medical Center, SMH: Santa Monica UCLA Hospital, ICU: Intensive Care Unit, Hosp.: Hospitalization, Advanced Ventilation: Either non-invasive mask ventilation or endotracheal

intubation, WBC: White Blood Cell count, BUN: Blood Urea Nitrogen, GFR: Race-adjusted Glomerular Filtration Rate, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALK: Alkaline Phosphatase, aPTT: Activated Prothrombin Time, INR: International Normalized Ratio, Anti-Pseudomonal Carbapenem: Meropenem, Imipenem, or Doripenem

Table 4-4: Model specifications for ErtaR-GNR (4a) and ColR-KP (4b)

ErtaR-GNR	Coefficient	Standard Error	p-value
Male gender	0.36	0.04	<0.001
Ventilated during index hospitalization	0.40	0.05	<0.001
Tracheostomy present	0.70	0.07	<0.001
Carbapenems within 30 days	0.60	0.05	<0.001
Anti-MRSA agents within 30 days	0.49	0.05	<0.001
ACR-GNR	**Coefficient**	**Standard Error**	**p-value**
Male gender	0.30	0.05	<0.001
In facility prior to admission	0.71	0.06	<0.001
Ventilated during index hospitalization	0.96	0.06	<0.001
Hemoglobin >11 g/dL	-0.49	0.07	<0.001
Carbapenems within 30 days	1.37	0.05	<0.001

Table 4-5: Percentage of ER-GNR having each score and percentage resistant at each score

Score	Percent of total organisms with score	Resistance rate at score
0	29.4%	8.7%
1	29.6%	17.8%
2	20.5%	23.8%
3	12.8%	33.0%
4	5.7%	42.1%
5	1.9%	59.0%

Table 4-6: Percentage of ACR-GNR having each score and percentage resistant at each score

Score	Percent of total organisms with score	Resistance rate at score
0	14.1%	1.1%
1	32.5%	2.6%
2	28.1%	5.4%
3	17.4%	10.9%
4	6.8%	18.5%
5	1.2%	41.9%

Chapter 5 - Risk factors for development of aminoglycoside resistance among gram-negative rods

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Abstract

Infections due to aminoglycoside-resistant gram-negative rods (AR-GNR) are increasing in frequency and result in high morbidity and mortality. Appropriate initial antibiotic therapy is necessary to reduce adverse consequences and shorten length of stay. To determine risk factors for recovery on culture of AR-GNR, cases were retrospectively analyzed at a major academic hospital system from 2011-2016. Gentamicin and tobramycin resistance (GTR-GNR) and amikacin resistance (AmR-GNR) patterns were analyzed separately. A total of 26,154 GNR isolates from 12,516 patients were analyzed, 6,699 (25.6%) of which were GTR, and 2,467 (9.4%) of which were AmR. In multivariate analysis, risk factors for GTR-GNR were presence of weight loss (as measured by the Elixhauser Score category) admission from another medical or long-term care facility, hemoglobin <11, receipt of any carbapenem in the prior 30 days, and receipt of any fluoroquinolone in the prior 30 days (c-statistic of 0.63). Risk factors for AmR-GNR were diagnosis of cystic fibrosis, male sex, admission from another medical or long-term care facility, ventilation at any point prior to culture during the index hospitalization, receipt of any carbapenem in the prior 30 days, and receipt of any anti-MRSA agent in the prior 30 days (c-statistic of 0.74). Multinomial and ordinal models demonstrated that the risk factors for the two resistance patterns differed significantly. A scoring system derived from these models can be applied by humans to guide empiric antimicrobial therapy, and outperformed use of a standard hospital antibiogram in predicting infections with GTR-GNR and AmR-GNR.

Keywords: Antimicrobial resistance, clinical decision making, antimicrobial testing, antimicrobial stewardship, aminoglycosides, gram-negative rods

Introduction

Rising worldwide prevalence of human infections with multi-drug resistant organisms (MDROs) is associated with increasing morbidity, mortality, and cost.[2] In the US, there are approximately 23,000 yearly attributable deaths and $50 million in yearly attributable costs from MDRO infections.[1] Appropriate initial antibiotic therapy decreases mortality and hospital length of stay,[8,9] while overuse of broad-spectrum antibiotics has been linked with increased prevalence of MDROs;[15-19] the initial choice of antibiotic remains a challenging and high-stakes decision.

Aminoglycosides are a class of antibiotics typically reserved for treatment of isolates resistant to beta-lactams and other first-line antibiotic classes. Aminoglycoside resistance among gram-negative rods (AR-GNRs) has been increasing over the past several decades.[67-69] Aminoglycoside resistance typically co-occurs with resistance to other antibiotics,[70,71] increasing the risk for inappropriate initial antibiotic therapy, which has been shown to increase length of stay and mortality.[6,10,12,66] However, early identification of AR-GNR can be challenging, as risk factors have not been consistently identified in the literature and this information is not available on initial culture results.

Prior literature on risk factors for aminoglycoside-resistant infections has been sparse, and has focused as much on gram-positive cocci as on GNRs. Several risk factors have been identified, primarily exposure to aminoglycosides,[70,72-74] higher level of care,[72] and presence of indwelling devices and exposure to other antibiotics.[71,75] Other risk factors for development of

MDROs in general included prior residence in a nursing home, hemodialysis, ICU admission,[34] increased medical comorbidity,[49,56] prior antibiotic usage, and invasive surgery.[56]

Compared to gentamicin and tobramycin (gent/tobra), amikacin typically has higher rates of non-susceptibility.[67,69,76] It is unclear from prior literature if the risk factors for gent/tobra resistance (GTR) are the same as for amikacin resistance (AmR). As such, two separate analyses were performed, one examining risk factors for GTR-GNR, and one for AmR-GNR, to examine the similarities and differences in risk factors for recovery of a non-susceptible isolate. This was followed by an analysis to determine if the risk factors were similar enough that a single model could predict resistance to both.

We hypothesized that a large, adequately powered study would provide sufficient observations to identify easily obtainable clinical factors that could serve as prediction tool for identifying patients at high risk for acquiring AR-GNRs.

Methods

We conducted a retrospective study of all patients with positive cultures from any source over a six-year period to develop a comprehensive model for risk of infection or colonization with AR-GNRs, with separate analyses for GTR-GNR and AmR-GNR. The study was performed at two hospitals in metropolitan Los Angeles, California. Ronald Reagan UCLA Medical Center is a 520-bed tertiary care center with five adult intensive care units totaling 109 beds, Santa

Monica-UCLA Medical Center has 266 beds total with 22 mixed intensive care beds in a single unit. Both are part of UCLA Health and serve patients with solid organ and bone marrow transplants, cancer, and various medical and surgical conditions. The Integrated Clinical and Research Data Repository (xDR) serves as a warehouse for all clinical data in the UCLA system since the implementation of electronic health records in 2006. The initial dataset contained information from all admissions with start dates from January 2006 through November 2016 to either hospital for patients ≥18 years of age and at least one positive culture from any source (blood, urine, sputum, wound cultures, or other fluids).

Since the endpoint of this analysis was prediction of development of the first aminoglycoside non-susceptible isolate, once a patient had a culture growing an organism with non-susceptibility to the antibiotic in question, defined using Clinical and Laboratory Standards Institute (CLSI), breakpoints current to the year of testing, all cultures from that patient occurring at a later time than the original culture were removed from the dataset. Since gentamicin and tobramycin had significant overlap in resistance patterns and neither drug was consistently more effective than the other, gentamycin and tobramycin resistance were treated as a single entity, with an organism treated as GTR if it had resistance to either gentamicin or tobramycin.

Routine susceptibility testing was performed by the CLSI reference broth microdilution method (BMD), using panels prepared in-house. Only data from 2011 and onwards were used in this study, as a changeover in clinical data warehousing methods corresponded to significantly more robust clinical

information after that time. All antimicrobial susceptibility data were interpreted using CLSI breakpoints current to the year of testing. Isolates with intrinsic non-susceptibility to the studied antibiotics were included in the analysis as non-susceptible cultures.

Predictor variables were chosen on the basis of prior studies, as well as those with biologic plausibility that were readily obtained from the medical record. Risk factors were identified in the literature through a partially structured search of PubMed and Google Scholar. For PubMed, the initial search used the phrase: (aminoglycoside OR gentamicin OR tobramycin OR amikacin) AND (resist* OR non-suscept* OR suscept* OR nonsuscept* OR sensiti* OR non-sensiti* OR nonsensiti*) AND (risk OR predict* OR protec*). For Google Scholar, the initial search used the phrase: (aminoglycoside | gentamicin | tobramycin | amikacin) (resist* | non-suscept* | nonsuscept* | suscept* | sensiti* | non-sensiti* | nonsensiti*) (risk factors | predict* | protect*). Once initial articles were identified, the references cited in those articles were also explored iteratively.

Data collected for each patient included admission hospital, days since admission, location prior to admission (home vs. long-term care facility or other hospital), demographic information, comorbidities (grouped into categories based on Elixhauser score designations),[57] laboratory results from the date of the culture, vital signs on the date the culture was collected (maximum temperature, heart rate, and respiratory rate, and minimum blood pressure), vital signs from initial hospital presentation, oxygen/ventilation method, presence of a tracheostomy, presence of urinary catheter, administration of antibiotics and

other selected medications (vasopressors, probiotics, blood products, immunosuppressants, and acid suppressants), and culture source.

Administration of antibiotics and the medications listed above was coded as the number of days since last receipt of the medication, Winsorized to a maximum value of 100 (received within 24 hours of the time of culture = 0, never received was coded as 100 days since receipt). “Anti-MRSA” agents refers to vancomycin, linezolid, and daptomycin, as these were used at our institution in cases of suspected hospital-acquired MRSA. Receipt of antibiotics were by any route, including oral, intravenous, and inhaled. An infection was coded as “hospital acquired” if the culture was submitted to the laboratory >48 hours after the time of first presentation to the hospital. The construct of advanced ventilatory support includes patients receiving either non-invasive or invasive mechanical ventilation.

In cases where laboratory tests were not performed before cultures were sent (typically at the beginning of a patient’s admission), the first set of laboratory results were used for that patient, provided they were performed on specimens collected within 24 hours of culture positivity. For laboratory tests not typically performed daily (e.g., liver function tests, measures of coagulation, and protein/prealbumin), the most recent result within a 48-hour period prior to culture positivity was used.

To facilitate model interpretability, some linear variables were recategorized as binary variables using cutoffs. Various cutoffs were tested against each other in the final model (e.g. 30 vs. 60 vs. 90 days since receipt of

last antibiotic), and the cutoff that led to the highest c-statistic was chosen for inclusion in the scoring system.

Statistical Analysis

Two separate analyses were performed, one comparing all gent/tobra-sensitive GNRs (GTS-GNR) against GTR-GNR, and one comparing amikacin-susceptible GNR (AmS-GNR) against AMR-GNR. These analyses were chosen to aid decision at the point of initial antibiotic choice, when the consequences for inappropriate antibiotic therapy are the greatest.[6,10,12,66] The measured variables in each case were compared between the cases and controls by a two-sided Mann-Whitney U test, Student's t-test, or chi-squared test, as appropriate. In each case, after bivariate associations were examined, variables with $p<0.10$ or strong biologic plausibility were included in a stepwise forward model selection procedure to create a logistic regression model for each analysis. Only complete cases were included in model selection. Model discrimination was assessed with area under the receiver operating characteristic curve (c-statistic), and models were compared by chi-squared test if they were nested, or Akaike information criterion if they were not.

The steps of the model selection strategy are detailed in Appendix C. In each case, the predictor variables were divided into several categories, comprising medical comorbidities, demographics (age, gender, race, location prior to admission, and social history), laboratory variables, indwelling devices, and received medications. Vital signs as a group lacked sufficient explanatory

power to be included in the model. Model selection occurred in stages, with each stage involving either the introduction of a new category of predictor, or the combination of a new category with prior models. At each stage, candidate variables from the chosen new category (defined as those with $p < 0.05$ on bivariate analysis or those with $p < 0.10$ with support from prior literature) were added to an initial model, and those that became non-significant in the multivariate model were dropped. Next, variables were iteratively dropped in a backwards selection process until parsimony was achieved. A parsimonious model was defined as the model with the smallest set of predictors in which dropping additional predictors resulted in a substantial drop in AUROC. A substantial drop in AUROC was defined as a decrease of at least 0.02, and a decrease that was larger by a factor of two than the decrease in AUROC with dropping the prior, less explanatory variable. In situations with two highly correlated variables that related to closely related constructs (for example, whether a patient was currently ventilated and whether they were ventilated at any point during the index hospitalization), the variable with less explanatory power was dropped, as measured by change in AUROC. The exceptions to the above process were some laboratory values, as there were a large number of laboratory values that were significant at $p < 0.05$ on bivariate analysis despite not having a clinically significant difference between the resistant and non-resistant groups. In these cases, the laboratory values with $p < 0.05$ were added individually to the final model to assess if they contributed significantly to the explanatory power (as defined by AUROC increase of 0.02); none of them did,

and none were included.

For GTR-GNR, model selection began with the list of relevant medical comorbidities. Once this list was pared to a parsimonious model, demographic information was added and the model was pared again (Table C-1). Next, a model was constructed using only laboratory variables and, once pared, this model was combined with the final model from the previous table (Table C-2). Finally, a model was constructed using recently administered medications, and this was pared and combined with the previous predictors (Table C-3). Indwelling devices did not have sufficient explanatory power to contribute to the multivariate model when combined with the other predictors.

For AmR-GNR, model selection began with the list of relevant medical comorbidities. Once this list was pared to a parsimonious model, demographic information was added and the model was pared again (Table C-5). Next, relevant indwelling devices were added to the model and the model was pared (Table C-6). Then, a model was constructed using only laboratory variables and, once pared, this model was combined with the final model from the previous table (Table C-7). Finally, a model was constructed using recently administered medications, and this was pared and combined with the previous predictors (Tables C-8).

For the combined model, three categories were created - susceptible to all aminoglycosides, GTR but not AmR, and AmR. If an isolate was non-susceptible to amikacin but susceptible to gent/tobra, it was classified as AmR, as though it were also sensitive to gent/tobra; these isolates comprised <3% of the total AmR

isolates. Multinomial and ordinal logistic regression models were then fitted predicting all three outcome categories, and these models were tested against each other by AIC. The Brant test was used to determine if the proportional odds assumption held for the ordinal model. All analyses were performed using the Stata statistical software package, version 14.2.[58]

Results

The complete dataset included 26,154 GNR isolates from 12,516 patients, 6,699 (25.6%) of which were GTR, and 2,467 (9.4%) of which were AmR. Since only complete cases were analyzed for the multivariate model, the final model for ER comprised 12,457 cultures, 1,779 (14.3%) of which were GTR-GNR, and the final model for AmR comprised 12,062 cultures, 532 (4.4%) of which were AmR-GNR. The multinomial model comprised 12,062 cultures, 1,973 (16.4%) of which were GTR-GNR but not AmR-GNR, and 532 (4.4%) of which were AmR-GNR.

The majority of GTR-GNR were *Escherichia* species, while the most common GTS-GNR were *Escherichia* and *Pseudomonas* species; the most common AmR-GNR were *Stenotrophomonas* species (which have intrinsic resistance), while the most common AmS-GNR were *Escherichia* species (Table 5-1). Respiratory culture source was predictive of both GTR-GNR and AmR-GNR, while urinary source was predictive of both GTS-GNR and AmS-GNR (Table 5-2).

Bivariate Analyses

Selected bivariate associations are reported in Table 5-3. Male sex and Black American race were significantly associated with both GTR and AmR. The most strongly associated comorbidities associated with both GTR and AmR were cystic fibrosis and the Elixhauser score categories of weight loss and chronic pulmonary disease. In general, medical comorbidities were more strongly associated with GTR than AmR, while measures of disease severity (longer length of stay, higher white blood cell count, presence of septic shock, and presence of invasive ventilation or devices) were more strongly associated with AmR than GTR. Non-hematologic laboratory values were inconsistently associated with either resistance pattern. Consistent with prior literature, recent administration of aminoglycosides[70,72-74] and other antibiotics[71,75] was predictive of both GTR and AmR.

Multivariate Analyses

Many of the variables that were significant on bivariate analysis were strongly co-linear, and thus were categorized into our model as three major constructs representing chronic illness, antibiotic exposure, and acute illness. To facilitate model interpretability, the variables representing days since receipt of medications were dichotomized to receipt within the prior 30 days vs. not; this did not significantly affect model fit. Hemoglobin was tested at multiple thresholds from 7-13g/dL; a cutoff of 11g/dL was found to have the best model discrimination.

For the model predicting GTR-GNR, the predictors in the final model were

presence of weight loss (as measured by the Elixhauser Score category),[57] admission from another medical or long-term care facility, hemoglobin <11, receipt of any carbapenem in the prior 30 days, and receipt of any fluoroquinolone in the prior 30 days; this model had a c-statistic of 0.63 (Table 5-4a).

For the model predicting AmR-GNR, the predictors in the final model were somewhat overlapping: diagnosis of cystic fibrosis, male sex, admission from another medical or long-term care facility, ventilation at any point prior to culture during the index hospitalization, receipt of any carbapenem in the prior 30 days, and receipt of any anti-MRSA agent in the prior 30 days; this model had a c-statistic of 0.74 (Table 5-4b).

Treating each multivariate model as a score with one point assigned for each of the items in the model, we created a potentially user-friendly tool to predict the probability of GTR and AmR. Figures 5-1 and 5-2 show the positive predictive value at each score total for GTR and AmR, respectively, and demonstrate that higher score is associated with higher likelihood of resistance. Rates of GTR range from 10.2% for a score of 0 to 32.1% at a score of 4+. Rates of AmR range from 0.7% at a score of 0 to 17.3% at a score of 5; there were 0 cases with a score of 6. Tables 5-5 and 5-6 show the fraction of GNR with each score for gentamicin/tobramycin and amikacin resistance, respectively, and the positive predictive value for resistance at each score. There were no isolates with an AmR-GNR score of 6. Only 5 GNR isolates had a GTR-GNR score of 5, 1 of which was resistant. Due to the small sample size at this score and the unusually

low rate observed in that small sample, the GTR-GNR scores of 4 and 5 were combined into a single estimate for the figure and final scoring system.

Alternate scoring systems were tested for each model, with separate models assigning scoring weights in proportion to the model coefficients and in proportion to the change in odds ratios. In each case the range of predicted probabilities of resistance was similar between the upper and lower bounds of the score, but there was more granular resolution of those probabilities as a result of a larger number of possible score totals. A flat scoring system (one point per factor) was ultimately chosen for ease of interpretability by providers.

Multinomial and Ordinal Logistic Regression

The risk factors for the GTR-GNR and AmR-GNR models were combined to create an (unordered) multinomial logistic regression and an ordinal logistic regression model predicting the three categories of aminoglycoside-susceptible, gent/tobra-resistant-amikacin-susceptible, and amikacin-resistant. By AIC, the multinomial model significantly outperformed the ordinal model. The Brant test of the proportional odds assumption indicated that the ordinal model did not appropriately describe the data. Taken together, these indicate that the risk factors for GTR-GNR differ from those for AmR-GNR in kind, and not merely degree.

Discussion

Inappropriate initial antibiotic treatment is associated with substantially increased cost and risk for mortality,[6,10,12,66] and appropriate antibiotic treatment is paramount in mitigating these risks. Prior studies of risk factors for AR among GNRs have largely focused on the family *Enterobacteriaceae*, which includes many commonly treated GNRs, but excludes several clinically significant species, including *Pseudomonas* and *Acinetobacter*. Additionally, many of these studies have been limited in scope (analyzing <200 total patients), and none have created a predictive scoring system.[70-72,75] Our scores can be calculated by humans at the time of decision-making and potentially more accurately reflects a patient's risk for aminoglycoside-resistant organisms than a hospital-wide or unit-specific antibiogram, which provides a flat percent observed susceptibility for a given organism in the prior year, and is not useful for management of rare events. All information used in the models was extracted directly from the medical record without any direct examination of individual patient records, allowing this score to potentially be calculated automatically.

Our bivariate analysis is consistent with prior studies, confirming associations between AR and receipt of mechanical ventilation and presence of various indwelling devices,[71,75] longer hospital stay and more severe illness at the time of culture,[72] and recent exposure to various antibiotics.[70-73,75] While it is improbable that exposure to all antibiotics mechanistically leads to development of AR, some of these exposures likely proxy recent infection with MDR GNRs, while anti-MRSA receipt proxies recent concern for sepsis, as nearly all patients with suspicion for sepsis receive at least one dose of vancomycin at our

institution. The conceptual model described in Chapter 2 suggests that acute illness does not play a large role in determining risk for recovery of a non-susceptible isolate on culture, and that the majority of risk occurs as a result of chronic illness and recent exposure to antibiotics. This analysis supports that conclusion in several ways. First, vital signs have limited predictive power, and while some variables related to blood pressure are significant on bivariate analysis (Table 5-3), none were included in the final model. Secondly, while laboratory values individually have predictive power on bivariate analysis (Table 5-3), all except for hemoglobin drop out when added to prior variables in the analysis (Tables C-2 and C-7). The only laboratory value with substantial predictive power is hemoglobin (which is included in the final model for GTR-GNR); low hemoglobin in this context is likely more related to chronic anemia than acute blood loss. Variables associated with chronic illness feature prominently in the models. In both models, chronic weight loss (which is associated chronic disease and malnutrition) and cystic fibrosis are significant medical comorbidities (Tables C-1 and C-5). In the GTR-GNR model, weight loss features in the final specification; in the AmR-GNR model, cystic fibrosis features in the final specification. The final model for GTR-GNR comprises recent antibiotic exposure and markers of chronic illness: weight loss, anemia, and transfer from another medical facility (Table C-4). The final model for AmR-GNR comprises male gender, recent antibiotic exposure, cystic fibrosis, transfer from another medical facility, and ventilation during the current hospital stay. While ventilation during the current hospital stay in both cases could proxy both acute

and chronic illness, the majority of other risk factors in the model are more associated with chronic illness as opposed to acute decompensation.

The discrimination ability for the GTR-GNR model is more limited than for the AmR-GNR model, likely because the populations susceptible to GTS-GNR and GTR-GNR are relatively similar. GTR is substantially more common than AmR, and infections by these organisms are likely driven more by random chance than is acquisition of an AmR organism. The final model for AmR-GNR risk contains variables that are more relevant to chronic respiratory failure and prior severe infections, which are likely indicative of exposure to multiple antibiotics and repeated infections with organisms capable of developing AmR. Additionally, the combined analysis indicates that the risk factors, while overlapping, are significantly different for the two resistance patterns. The model discrimination for the AmR-GNR model is substantially better than for the GTR-GNR model, indicating that the populations susceptible to AmR (vs. AmS) GNR infections differ in more identifiable ways; as such, the model is more able to rule out AmR-GNR infections at lower scores, with a <5% risk for AmR-GNR infection at scores <3.

Our study has limitations. It examines patients from only two hospitals within a single hospital system. After eliminating duplicate cultures, approximately 60% of GTR and AmR-GNR cases could not be included in the final analysis due to a lack of complete data across the relevant domains. Additionally, we only had access to data from inpatient hospitalizations within our hospital system, potentially excluding relevant information from outpatient

encounters or treatment at other facilities. These limitations reflect the real-world data that is available at the time of decision-making, or for eventual integration of a similar score into an electronic health record. However, it is the largest investigation to date in terms of subject number and spans a period of six years, allowing us to examine far more potential explanatory variables than prior investigations of risk factors for development of GTR-GNR and AmR-GNR. By performing a cohort study of patients with positive cultures, we eliminate potential selection bias in choosing controls and strengthen the validity of observed associations.[60]

While the discriminatory capacity of the GTR-GNR model is limited, the AmR-GNR model can effectively rule out AmR risk (<5% chance) at scores <2, allowing reasonably confident treatment with amikacin as a first option without waiting for definitive amikacin susceptibility testing, which can take up to several days.

Our study demonstrates the potential to harness currently available information from an existing electronic medical record to inform clinical decision-makers. Our simplified scoring system clearly outperformed the traditional antibiogram approach of offering a single hospital-wide percentage rate of susceptibility, by creating an individualized score than can be used and interpreted by individual clinicians without computer assistance. In the current era of data intensive medical care, we should harness all available information to better manage our patients. Further research will focus on validating this score in

other populations, and analysis of cost-benefit thresholds for initiating specific antibiotic regimens in cases of uncertainty.

Figure 5-1: Positive predictive value for gentamicin/tobramycin resistance at each score value for gram-negative rods

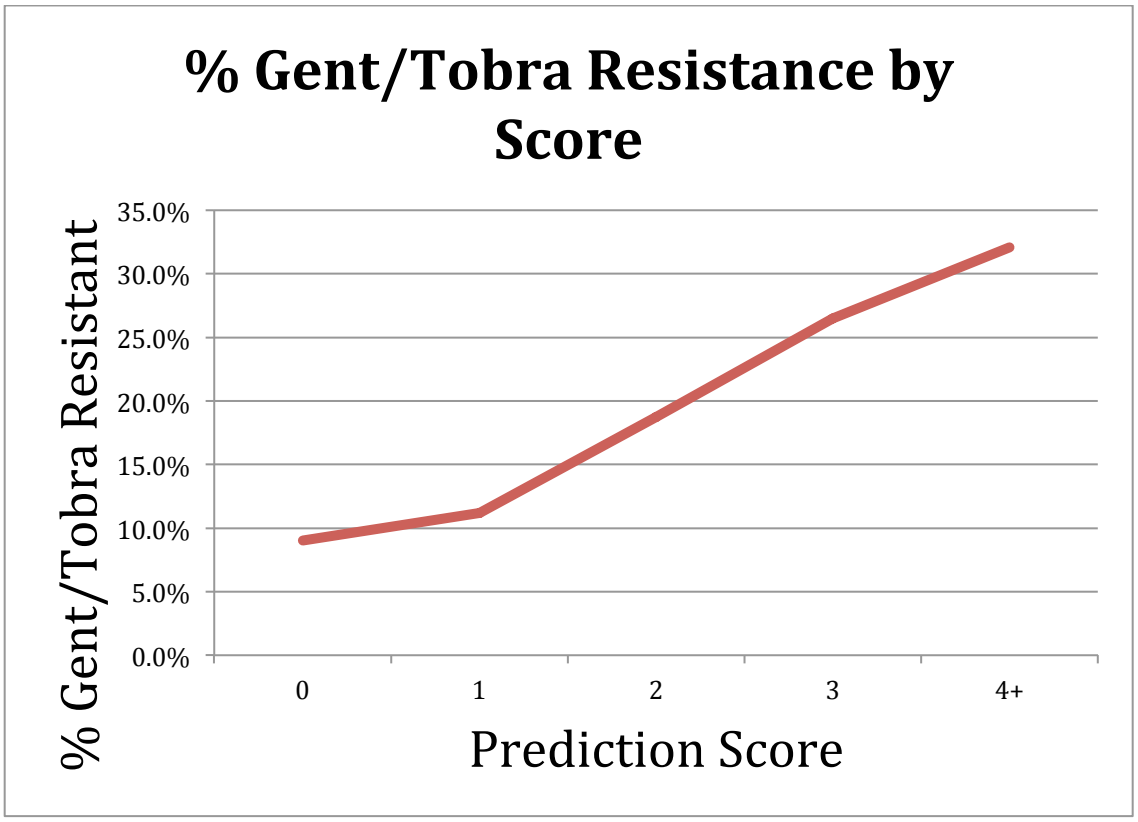

Figure 5-2: Positive predictive value for amikacin resistance at each score value for gram-negative rods

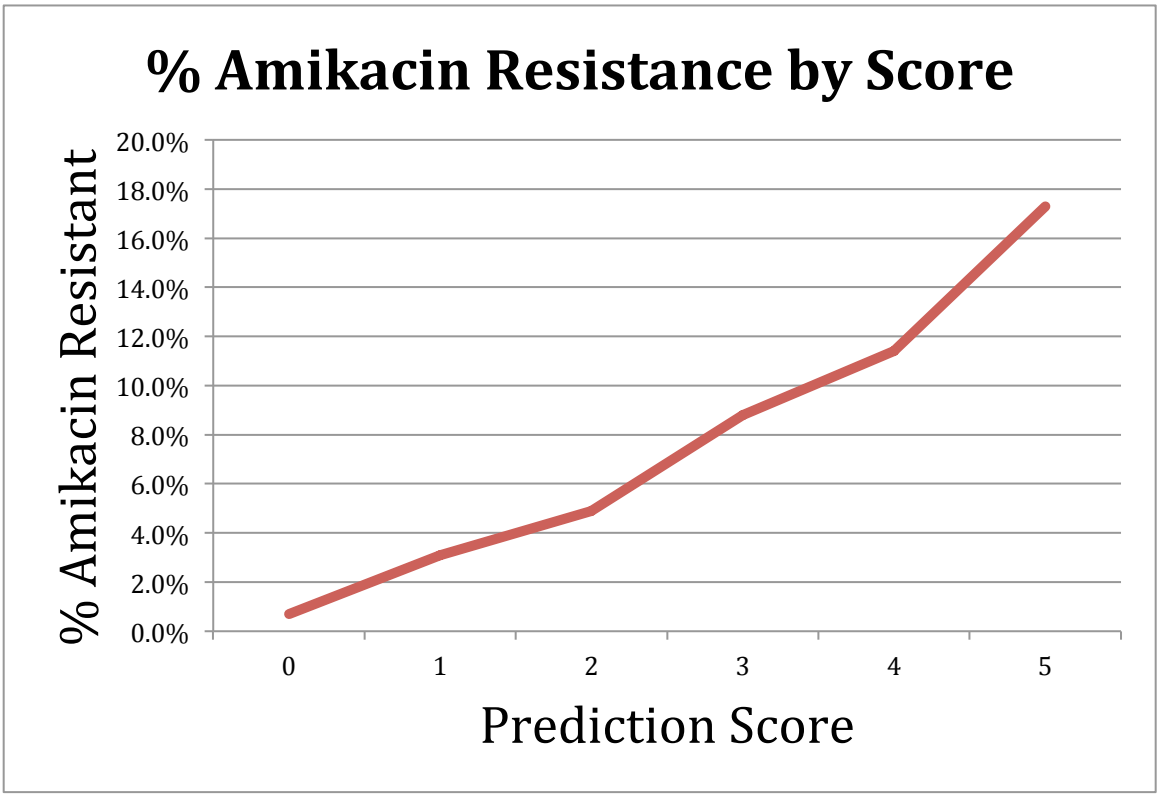

Table 5-1: Distribution of organisms for GTS-GNR, GTR-GNR, AmS-GNR, and AmS-GNR ($p < 0.001$ for X^2 test for both ER and AmR)

organism	GTS	GTR	AmS	AmR
Acinetobacter	1.0%	6.5%	1.0%	14.5%
Enterobacter	9.5%	1.2%	9.0%	0.2%
Escherichia	34.9%	33.4%	40.7%	4.6%
Klebsiella	17.8%	13.4%	18.4%	15.4%
Pseudomonas	21.7%	13.6%	13.9%	14.1%
Stenotrophomonas	0.0%	16.0%	0.0%	43.5%
Other	15.1%	15.9%	17.0%	7.7%

Table 5-2: Distribution of culture source for GTS-GNR, GTR-GNR, AmS-GNR, and AmS-GNR ($p < 0.001$ for X^2 test for both ER and AmR)

Source	GTS	GTR	AmS	AmR
Blood	8.8%	9.3%	8.9%	9.1%
Urine	46.2%	34.3%	48.4%	10.8%
Respiratory	24.0%	38.9%	22.8%	62.5%
External	7.8%	7.6%	7.5%	7.5%
Other	13.2%	10.0%	12.4%	10.2%

Table 5-3: Selected bivariate associations

	GTS-GNR	GTR-GNR		AmS-GNR	AmR-GNR	
n =	21,540	4,087	p-value	23,687	1,315	p-value
Age	64.2(19.1)	65.6(18.7)	<0.001	64.7(19)	62.4(19)	<0.001
Male Sex	45.4%	49.2%	<0.001	44.6%	56.7%	<0.001
Race			<0.001			0.011
White	53.7%	50.4%		52.5%	53.8%	
Asian	9.0%	7.5%		8.9%	8.0%	
Black	11.1%	13.7%		11.5%	13.0%	
Latino	20.0%	20.8%		20.8%	17.6%	
Other	6.1%	7.6%		6.4%	7.7%	
BMI	26(6.7)	25.5(6.8)	<0.001	26.1(6.8)	25.1(6.6)	<0.001
Admitted From Healthcare Facility	14.2%	28.5%	<0.001	16.2%	25.7%	<0.001
Hospital (RRMC vs. SMH)	65.6%	51.5%	<0.001	63.2%	53.6%	<0.001
Log Days To Culture	0.44 [-1.51,2.11]	0.57 [-1.41,2.35]	<0.001	0.36 [-1.57,2.11]	1.32 [-0.58,2.69]	<0.001
Hospital Acquired	43.0%	43.2%	0.841	42.1%	55.5%	<0.001
In ICU At The Time Of Culture	18.4%	18.7%	0.656	17.8%	25.8%	<0.001
Any ICU Stay During Index Hosp.	36.2%	41.6%	<0.001	35.7%	56.6%	<0.001
Presence of Indwelling Urinary Catheter	42.8%	50.3%	<0.001	43.8%	65.8%	<0.001
Ventilated During Index Hosp.	28.6%	38.7%	<0.001	28.5%	53.4%	<0.001
Tracheostomy Present On Day Of Culture	10.5%	17.8%	<0.001	10.7%	21.9%	<0.001
Tracheostomy Present On Admission	4.5%	10.8%	<0.001	4.8%	13%	<0.001
Advanced Ventilation On Day Of Culture	21%	28.9%	<0.001	20.8%	41.8%	<0.001
Elixhauser Score	15[6,26]	19[9,29]	<0.001	16[6,26]	21[11,30]	<0.001
Congestive Heart Failure	19.4%	24.9%	<0.001	20.3%	25.6%	<0.001
Arrhythmia	40.9%	49.5%	<0.001	42%	52.4%	<0.001
Valvular Disease	23.4%	27.2%	<0.001	24%	29.6%	<0.001
Pulmonary Vascular Disease	15.6%	19.1%	<0.001	16.1%	22.1%	<0.001
Peripheral Vascular Disease	22.8%	26.7%	<0.001	23.2%	28%	<0.001
Paralysis	7.5%	9.4%	<0.001	7.9%	8.7%	0.292
Neurologic Disease	27.6%	37.9%	<0.001	28.8%	38.9%	<0.001
Chronic Pulmonary Disease	23.6%	31.6%	<0.001	24.6%	35.5%	<0.001
Renal Disease	32.2%	39.2%	<0.001	33.5%	39.6%	<0.001
Liver Disease	23.8%	25.4%	0.021	24.5%	27.9%	0.005
Lymphoma	4.1%	4.4%	0.313	4.1%	4.9%	0.152

Metastatic Cancer	10.6%	8.2%	<0.001	10.1%	9.7%	0.687
Non-Metastatic Cancer	23.4%	18.8%	<0.001	22.8%	20.6%	0.067
Coagulopathy	25%	30.7%	<0.001	26%	32.9%	<0.001
Weight Loss	17.2%	25.7%	<0.001	18%	30.5%	<0.001
Electrolyte Disorder	58.7%	66.8%	<0.001	60.3%	70%	<0.001
Deficiency Anemia	12.8%	14.9%	<0.001	13.3%	13.8%	0.635
Drug Abuse	6.7%	6.3%	0.330	6.8%	6.8%	0.933
Depression	22.5%	25.5%	<0.001	23.4%	25%	0.179
Solid Organ Transplant	16.9%	17.2%	0.669	17.3%	18.3%	0.378
Bone Marrow Transplant	1.3%	1.5%	0.255	1.2%	1.9%	0.018
Renal Failure	13.5%	17.7%	<0.001	14.5%	18.3%	<0.001
Cystic fibrosis	0.8%	2.3%	<0.001	0.7%	5.5%	<0.001
HIV	0.8%	0.8%	0.990	0.8%	0.8%	0.988
Alcohol User	23.3%	17.3%	<0.001	22%	19.3%	0.077
Tobacco User	5.9%	5.1%	0.123	5.7%	4.5%	0.154
Vital Signs On Day Of Culture						
Maximum Temperature	99.6(1.6)	99.5(1.6)	0.026	99.6(1.6)	99.5(1.6)	0.415
Maximum Pulse	102.7(22.4)	102.9(22.4)	0.635	102.5(22.5)	105.9(22.3)	<0.001
Maximum Respiratory Rate	26.7(9.5)	27.5(9.7)	<0.001	26.7(9.5)	29.4(10.3)	<0.001
Minimum SBP	102.7(21.5)	100.6(22.5)	<0.001	102.7(21.7)	97.3(22.1)	<0.001
Minimum DBP	58.8(12.2)	57.9(13)	<0.001	58.7(12.4)	57(13)	<0.001
Minimum MAP	73.4(14.2)	72(15)	<0.001	73.3(14.3)	70.4(14.7)	<0.001
Septic Shock	18.9%	18.4%	0.392	18.9%	21.5%	0.019
Hypotensive	19.7%	19%	0.342	19.6%	22.1%	0.028
Labs On Day Of Culture	91.2(21.7)	92.7(22)	0.002	91.3(21.7)	94.2(21.7)	<0.001
WBC	12.4[8.7,17.1]	12.7[8.8,17.4]	0.061	12.3[8.7,17]	13.4 [9.4,18.5]	<0.001
Hemoglobin	10[8.7,11.6]	9.7[8.5,11.1]	<0.001	10[8.7,11.6]	9.3[8.3,10.6]	<0.001
Hematocrit	30.7 [26.8,35.3]	29.9 [26.3,34.1]	<0.001	30.7 [26.7,35.2]	29 [25.8,32.8]	<0.001
Platelets	206[134,289]	213[129,302]	0.046	205[133,288]	211[119,314]	0.224
Sodium	137(6)	138(6)	0.172	137(6)	138(6)	<0.001
Potassium	4.1(0.6)	4.1(0.6)	<0.001	4.1(0.6)	4.1(0.6)	0.398
Chloride	103(6)	102 (7)	0.107	103(7)	102 (7)	0.301
Bicarbonate	24.4(4.6)	24.8(5.1)	<0.001	24.4(4.6)	25.5(5.5)	<0.001
Anion Gap	10.4(4)	10.3(4.1)	0.414	10.4(4)	10.1(4.3)	0.014
Creatinine	1.4(1.3)	1.5(1.4)	<0.001	1.4(1.3)	1.4(1.3)	0.466
BUN	27.9(22.4)	32.2(26.3)	<0.001	28.4(22.7)	32.6(28)	<0.001
GFR	71[40,100]	68[36,100]	<0.001	70[39,100]	72[37,100]	0.160
Glucose	135(57)	136(61)	0.480	135 (59)	135(54)	0.686
Magnesium	1.7(0.3)	1.7(0.4)	0.006	1.7(0.3)	1.8(0.4)	<0.001
Calcium	8.6(0.8)	8.6(0.9)	0.565	8.6(0.8)	8.6(1.1)	0.248
Phosphorus	3.3(1.2)	3.4(1.2)	0.031	3.3(1.1)	3.4(1.2)	0.036

AST	68(352)	65(328)	0.735	66(335)	77(403)	0.286
ALT	51 (190)	49(167)	0.503	50(175)	51(156)	0.846
ALK	143(161)	153(163)	0.002	143(156)	164(187)	<0.001
aPTT	22.1(14.5)	23.5(15.5)	<0.001	22.3(14.9)	24.8(16.5)	<0.001
INR	1.3(0.6)	1.4(0.7)	0.004	1.3(0.6)	1.4(0.6)	0.055
Lactate	20.1(21.8)	19.6(20.2)	0.338	20.3(21.6)	19.4(21.8)	0.275
D-dimer	2972(2524)	2976 (2532)	0.976	3002(2536)	3051(2684)	0.821
Prealbumin	14.4(8.1)	14.2(7.8)	0.462	14.3(8.1)	13.9(7.7)	0.212
Protein	6.1(1)	6.1(1.1)	0.284	6.1(1)	6(1.1)	<0.001
Fibrinogen	328(180)	328(179)	0.985	323(177)	337(191)	0.114
Days Since:						
Last Antibiotic	0[0,9]	0[0,4]	<0.001	0[0,9]	0[0,0]	<0.001
Last Aminoglycoside	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Carbapenem	100[100,100]	100[47,100]	<0.001	100[100,100]	100[4,100]	<0.001
Last Fluoroquinolone	100[100,100]	100[50,100]	<0.001	100[100,100]	100[21,100]	<0.001
Last Penicillin	100[2,100]	100[3,100]	0.150	100[3,100]	60[1,100]	<0.001
Last Anti-MRSA	100[0,100]	24[0,100]	<0.001	100[0,100]	4[0,100]	<0.001
Last Colistin	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Aztreonam	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Beta-lactam	0[0,100]	0[0,79.5]	0.089	0[0,100]	0[0,18]	<0.001
Last Acid Suppressant	0[0,100]	0[0,100]	<0.001	0[0,100]	0[0,2]	<0.001
Last Probiotic	100[100,100]	100[100,100]	<0.001	100[100,100]	100[100,100]	<0.001
Last Steroid	100[60,100]	100[22.5,100]	0.090	100[61,100]	100[4,100]	0.002
Last Chemotherapy	100[100,100]	100[100,100]	0.233	100[100,100]	100[100,100]	0.015
Last Immunosuppressant	100[2,100]	100[0.5,100]	0.312	100[2,100]	100[0,100]	0.021
Last Blood Product	100[100,100]	100[100,100]	0.001	100[100,100]	100[28,100]	<0.001

Normally-distributed outcomes are reported as mean(standard deviation), non-normally-distributed outcomes are reported as median[interquartile range]. Binary outcomes are reported as percent positive.

BMI: Body Mass Index, RRMC: Ronald Reagan Medical Center, SMH: Santa Monica UCLA Hospital, ICU: Intensive Care Unit, Hosp.: Hospitalization, Advanced Ventilation: Either non-invasive mask ventilation or endotracheal intubation, WBC: White Blood Cell count, BUN: Blood Urea Nitrogen, GFR: Race-adjusted Glomerular Filtration Rate, AST: Aspartate Aminotransferase,

ALT: Alanine Aminotransferase, ALK: Alkaline Phosphatase, aPTT: Activated Prothrombin Time, INR: International Normalized Ratio

Table 5-4: Model specifications for GTR-GNR (4a) and AmR-GNR (4b)

GTR-GNR	Coefficient	Standard Error	p-value
Weight Loss	0.41	0.07	<0.001
Facility prior to admission	0.84	0.06	<0.001
Hemoglobin <11 g/dL	0.23	0.06	<0.001
Carbapenems within 30 days	0.49	0.07	<0.001
Fluoroquinolones within 30 days	0.38	0.07	<0.001
AmR-GNR	**Coefficient**	**Standard Error**	**p-value**
Cystic Fibrosis	2.04	0.21	<0.001
Male	0.47	0.10	<0.001
Facility prior to admission	0.43	0.11	<0.001
Ventilated during hospitalization	0.70	0.10	<0.001
Carbapenems within 30 days	0.61	0.10	<0.001
Anti-MRSA agent within 30 days	0.53	0.10	<0.001

Table 5-5: Percentage of GTR-GNR having each score and percentage resistant at each score

Score	Percent of total organisms with score	Resistance rate at score
0	22.8%	9.0%
1	42.5%	11.2%
2	23.6%	18.8%
3	9.1%	26.5%
4	2.0%	32.4%
5	0.0%	20.0%

Table 5-6: Percentage of AmR-GNR having each score and percentage resistant at each score

Score	Percent of total organisms with score	Resistance rate at score
0	26.1%	0.7%
1	29.5%	3.1%
2	22.0%	4.9%
3	14.7%	8.8%
4	6.6%	11.4%
5	1.2%	17.3%

Chapter 6 - The cost-effectiveness of meropenem versus colistin in the initial empiric treatment of low and high acuity patients presenting with undifferentiated infections

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Abstract

Infections due to carbapenem-resistant gram-negative rods (CR-GNR) are increasing in frequency and result in high morbidity and mortality. The optimal empiric antibiotic strategy for patients with undifferentiated infections depends on the frequency of resistance, but analysis of specific thresholds for clinical decision-making have been poorly studied. To determine which factors have the largest effect on initial antibiotic choice, we performed a decision analysis on two theoretical cohorts of patients presenting for treatment with uncharacterized infections, one with low risk for mortality, who would have been admitted to a regular hospital ward (low acuity), and one with high risk for mortality (high acuity), who would have been admitted to the intensive care unit (ICU) with severe sepsis or septic shock. We compared two strategies of treating empirically with either meropenem or colistin and performed sensitivity analyses to determine which strategy was preferable in terms of cost (low acuity) and avoidance of mortality (high acuity strategy) under several willingness-to-pay thresholds. Under base case assumptions, the meropenem-first strategy dominated in low acuity patients at a meropenem resistance rate of up to 10.9%. In high acuity patients, the colistin strategy was preferable with a willingness-to-pay per avoided death as low as $46,231; at $468,750 per avoided death, the colistin-first strategy was preferable with meropenem resistance rates as low as 5.5%. The relative cost difference between the two strategies was small in terms of overall health system impact, with the colistin-first strategy costing $2.83 per-member per-year.

Keywords: Antimicrobial resistance, clinical decision making, antimicrobial testing, antimicrobial stewardship, carbapenems, Gram-negative rods

Introduction

Increasing prevalence of infections with multi-drug resistant organisms (MDROs) is responsible for increasing morbidity, mortality, and cost.[1] In the US alone there are approximately 23,000 yearly attributable deaths and $50 million in yearly attributable costs from MDRO infections.[2] Appropriate initial antibiotic therapy can decrease mortality[3-9] and hospital length of stay,[6,10-14] while overuse of broad-spectrum antibiotics has been linked with increased prevalence of MDROs.[15-19] As such, the initial choice of antibiotic remains a challenging and high-stakes decision.

Carbapenem resistance among gram-negative rods (CR-GNRs) has been increasing over the past several decades.[14,61-63] Infection with CR-GNR species is associated with higher mortality[14,61,63,64] and hospital costs,[14,62] although it appears that many of the adverse outcomes associated with CR-GNR are due to ineffective initial antibiotic therapy (IAT).[4-7] As such, effective initial antibiotic therapy (EAT) is paramount to reducing adverse outcomes.

Since there are negative consequences to both over- and under-treatment with initial antibiotic choice, the optimal strategy will depend on the prevalence of resistant bacteria. In situations with low rates of resistance, using overly broad antibiotics potentially exposes patients to increased side effects, costs, and future rates of resistance, whereas in situations with low rates of resistance, insufficiently powerful initial antibiotic therapy risks undertreating the infection, with increased length of stay and mortality risk. The exact cutoffs for

prevalence of resistance that influence this decision have been insufficiently studied.

We focused our research on a specific question: which factors are key in influencing antibiotic strategy in patients with gram-negative infections when choosing between empiric therapy with meropenem vs. colistin? Since the payoffs appear to be different between low and high acuity infections, we constructed two models, one for each scenario, to address this question.

Methods

Model overview

Using decision-analysis software,[77] we evaluated two hypothetical cohorts of patients presenting to hospital care for treatment of infection - one with low risk for mortality, who would have been admitted to a regular hospital ward and are referred to as the "low acuity" (LA) group, and one with high risk for mortality, who would have been admitted to the intensive care unit (ICU) with severe sepsis or septic shock, and are referred to as the "high acuity" (HA) group. Infections of various types (urinary tract infections, pneumonias, and bloodstream infections) were analyzed together as a single group since there were not sufficiently granular data for various infection types. The two separate populations were chosen because the risk for mortality and expected length of stay (LOS) have been shown to vary substantially depending on severity of infection. Specifically, literature has shown that the risk for mortality in LA infections is not substantially affected by timeliness of effective antibiotic

therapy,[6,10,11] while the mortality risk for HA infections is substantially increased by delayed initiation of effective antibiotic therapy.[3-9]

A simplified decision tree is shown in Figure 6-1. The trees representing the two scenarios were made with the following assumptions:

- Patients were given one of two strategies: (1) Initial treatment with meropenem, with a conversion to colistin if the initial therapy was found to be ineffective on susceptibility testing, or (2) Initial treatment with colistin for all patients.
- All patients will have a positive culture/susceptibility profile that allows guidance of future therapy.
- Susceptibilities come back after 72 hours, and include colistin susceptibility.
- Complications from therapy (renal injury, anemia, and encephalopathy) happen during the first 72 hours of therapy with a given antibiotic, if they are going to happen.
- Patients will be treated with a total of seven days of effective therapy. If initial therapy is ineffective, they will receive three days of ineffective therapy followed by seven days of effective therapy.
- In the case of colistin non-susceptibility, there is a single “secondary salvage” regimen with a fixed daily cost and no additional modeled rate of complications. In this model, this fixed cost represents the expected costs of any additional testing or complications from the secondary salvage regimen.
- If there is a complication from initial meropenem therapy, there is no additional calculated risk for that same complication from colistin salvage therapy, or at

least no additional cost associated with having that same complication from colistin salvage therapy.

- Costs are calculated as (cost per hospital day)*LOS + (cost per antibiotic day)*(length of therapy) + (cost of complication)*(presence of complication)
- Complications from therapy do not lead to additional LOS as calculated in the model; instead, these costs (including costs for longer LOS) are captured by the total costs attributable to each complication as indicated in the literature.
- Mortality is only modeled in the HA scenario, as there is insufficient evidence to suggest significantly increased mortality in LA patients with ineffective initial therapy.
- Complications with an associated mortality risk add a flat percentage risk of death.
- The model follows patients until hospital discharge or death. In order to avoid inappropriately censoring costs for patients who died, the expected cost of a patient who survives to hospital discharge in a given scenario is considered to be equivalent to the expected cost of a patient who died prior to hospital discharge.

These assumptions were made to allow for a level of complexity that would hopefully approximate real clinical experience, without adding so many possibilities that the uncertainty from the estimates would render the conclusions suspect.

Clinical Probability and Cost Estimates

Our models used probability and cost estimates derived from a review of

the medical literature. Costs were determined from a hospital-payer perspective. We derived base-case estimates from a search of English-language publications from January 2005 to the present using PubMed, targeting systematic reviews, meta-analyses, and cost-benefit/cost-effectiveness analyses addressing issues of expected costs and/or length of stay for patients presenting with UTIs, PNA, BSI, or unspecified infection type, with or without sepsis/septic shock, and the consequences of effective vs. ineffective initial antibiotic therapy. In order to get a pooled estimate for the base cost and length of stay (LOS) for the LA and HA types, a median value was chosen, weighted for the various types of infections. To determine the cost for a hospital day for LA and HA patients, the total cost per admission was divided by the expected LOS for correct therapy, on the assumption that the majority of cases in the literature were correctly treated. All costs were converted to 2017 dollars using medical CPI.[78] We then varied each estimate over a wide range for the sensitivity analysis, as described below. Table 6-1 lists the range in the literature, base estimate, range for sensitivity analysis, justification, and supporting references for each probability, cost, and LOS estimate.

Although many of the estimates in the models have multiple supporting references (Table 6-1), several have limited data. The rates of resistance to meropenem and colistin were taken from a database of cases at the authors' main institution over the prior 8 years, and the range for resistance rates represents the upper and lower rates determined by clinical scoring systems for predicting these resistance rates. (Richter 2018, unpublished data) Actual

acquisition costs for antibiotic regimens are difficult to find in the literature, but available at our institution and were taken from the UCLA 2017 Antibiotic Guide. The upper limit on cost for the colistin regimen ($500/day) is meant to account for not only colistin, but also other potential similar regimens (such as novel drugs or drug combinations) and the expected value of associated testing and complications. The daily cost of salvage therapy is difficult to ascertain since there are no universally agreed-upon regimens to treat colistin non-susceptible GNR infections. A daily cost of $400 was chosen to cover the cost of the antibiotics, consultation fee by the Infectious Disease physicians necessary to administer such a regimen, and the expected value of additional tests and complications associated with the regimen. The incremental increase in cost for the complications of anemia and mental status changes come from a single paper[79] that examined this exact question. The most comparable complication to drug-induced anemia was “Post-hemorrhagic and other acute anemia with transfusion”; since not all drug-associated anemia requires transfusion, a value of half the mean value listed in the paper was chosen as a reasonable estimate for the expected costs attributable to drug-associated anemia. The incremental increase in mortality from the complications of drug therapy (acute kidney injury, altered mental status, and anemia) are poorly studied in the literature. Of these, the best studied is acute kidney injury, although the majority of studies report large increases in mortality odds ratio (up to 3.7) since they include all types of kidney injury (including that requiring hemodialysis) and populations with relatively low mortality risk to begin with.[80-82] Ultimately the value used in this

study was chosen to be an OR of 1.3 for mortality relative to the base-case septic patient, or an incremental 7% absolute risk for death, since this corresponded to the type of mild renal injury typically associated with adverse drug reactions. Delirium appears to be more associated with a risk for adverse outcomes than a direct cause,[83] but a range of incremental absolute mortality increase of up to 5% was included in sensitivity analysis to account for uncertainty. Since there were no articles that directly addressed the question of increased incremental mortality risk from drug-associated anemia, a base-case estimate of 0% with a range of up to 5% in sensitivity analysis was chosen. Estimates with less certainty were varied over relatively larger ranges in the sensitivity analysis to account for the lack of precision in the initial estimates.

Cost-Effectiveness Outcomes

To determine a reasonable value for willingness-to-pay (WTP) per avoided death in the HA model, we multiplied expected quality-adjusted life years (QALYs) after hospitalization for severe sepsis by WTP per QALY. As a sensitivity analysis, we used three WTP per QALY estimates corresponding to the bottom ($32,000/QALY), median ($75,000/QALY), and top of the range ($200,000/QALY).

Budget Impact Model

While cost-effectiveness analyses address the question of strategies for individual patients, they do not account for prevalence of the disease process or

for total costs to an institution. In some cases, expensive therapies can be justified if they are only used on small subsets of the population; conversely, the overall institutional cost of any given intervention is substantially higher if it is applied to a highly prevalent condition. As such, we created a budget impact model to analyze the total cost of each strategy in a hypothetical hospital system covering 100,000 patients, with the overall outcome being the difference in the per-member per-year (PMPY) cost for each initial strategy under the LA and HA scenarios. This is given by:

(Average cost per patient for a given strategy)*(Yearly incidence of the presenting condition)

where the presenting conditions were presentation with an infection with a gram-negative rod either with or without accompanying severe sepsis.

Sensitivity Analyses

Table 6-1 lists the base-case probability and cost estimates and the ranges used in sensitivity analyses. To test the sensitivity of the results to the assumptions of the estimates, a multivariable sensitivity analysis (tornado analysis) was performed to rank-order the most influential variables on the cost outcome of each strategy. We then performed a two-way sensitivity analysis on the two variables most influential to cost to determine their effects on the dominant strategy for lowest cost for the LA scenario and dominant strategy at the three WTP per avoided death thresholds for the HA scenario.

Monte Carlo Analyses

Monte Carlo analyses were performed in each scenario to test the sensitivity of the model to assumptions regarding variable range. In the LA scenario the analysis focused on the cost-minimization model. In the HA model, Monte Carlo analyses were performed at each WTP threshold. In each case, a triangular distribution of values was used, with the center point at the base case estimate and the top and bottom of the distribution corresponding to the minimum and maximum range in Table 6-1. Given the influential effects of the rate of renal toxicity from colistin, a maximum value of 30% was used in Monte Carlo analyses to account for scenarios in which hospitals have less effective monitoring of colistin dosing and potentially higher rates of toxicity. Each analysis was performed using 1,000 trials.

Results

Low Acuity Scenario

Using the base-case probabilities and costs drawn from the available literature and shown in Table 6-1, the strategy of initial empiric therapy with meropenem has an expected cost of $364 less per patient ($11,989 for the colistin-first strategy vs. $11,625 for the meropenem-first strategy). Multivariable sensitivity analysis (Figure 6-2) showed significant effects across the tested ranges from four variables - daily cost of colistin therapy, probability of meropenem resistance, probability of renal injury from colistin therapy, and probability of encephalopathy from meropenem therapy. Two-way sensitivity

analysis on the daily cost of colistin therapy and probability of meropenem resistance is shown in Figure 6-3, demonstrating that a colistin-first strategy dominates in scenarios with high prevalence of meropenem resistance and relatively lower cost for colistin therapy. With a constant daily cost for colistin therapy, the meropenem-first strategy is less costly up to meropenem resistance rates of 10.9%.

Monte Carlo analysis showed that the meropenem-first strategy was the less expensive model 77% of the scenarios. Since only one outcome was examined, this made it the dominant strategy in those scenarios.

Assuming a yearly incidence for LA infections of 780/100,000 patients,[84-87] the meropenem-first strategy corresponds to a yearly savings of $283,920/100,000 patients per year, or $2.83 PMPY.

High Acuity Scenario

Using the base-case probabilities and costs shown in Table 6-1, the strategy of initial empiric therapy with meropenem has an expected cost of $37 less per patient ($30,012 for the colistin-first strategy vs. $29,975 for the meropenem-first strategy). The colistin-first strategy results in a lower mortality, with an incremental cost-effectiveness ratio (ICER) of $46,231/avoided death. Multivariable sensitivity analysis (Figure 6-4) looking at only cost showed the most significant effects again from the probability of meropenem resistance and the daily cost of colistin therapy. Since the cost differential was small between the two strategies, the dominant strategy was sensitive to a large number of

predictors. Two-way sensitivity analyses on the daily cost of colistin therapy and probability of meropenem resistance at a WTP per avoided death of $200,000, $468,750, and $1,250,000 are shown in Figures 6-5, 6-6, and 6-7, respectively. These two-way analyses demonstrate that a meropenem-first strategy dominates in situations of lower meropenem resistance (below ~5.5%) and a colistin-first strategy dominates in situation with higher prevalence of meropenem resistance (above ~12.8%); the dominant strategy between within that range depends on the cost of colistin therapy and WTP per avoided death.

Monte Carlo analysis showed the colistin-first strategy was more cost effective in 73.0%, 81.1%, and 85.4% of the scenarios at a WTP of $200,000, $468,750, and $1,250,000, respectively.

Assuming a yearly incidence for HA infections of 300/100,000 patients,[87,88] the colistin-first strategy costs an additional $11,100/100,000 patients per year, or $0.11 PMPY.

Discussion

In the absence of published trials directly addressing the cost-effectiveness of different strategies for initial antibiotic therapy, an analysis such as this can help answer questions regarding the economic effects of optimal initial antibiotic therapy for patients presenting with undifferentiated gram-negative rod infections.

Assuming a 6% prevalence of meropenem resistance, a meropenem-first strategy dominates on the basis of cost for LA patients. The 6% prevalence

figure comes from the UCLA dataset used in Project 1, and is comparable to other recently published literature showing a carbapenem resistance rate of 4.5% over the time period 2009-2013,[89] when accounting for yearly increases in carbapenem resistance. However, with >10.9% prevalence of meropenem resistance, the colistin-first strategy becomes favorable (Figure 6-2). A clinical risk score to predict the probability of meropenem resistance for hospitalized patients was recently developed by several of the authors (Richter 2018, submitted for publication) and gives a range of probabilities for resistance ranging from 2-30% based on clinical information available at the time of decisions regarding initial therapy, which would allow clinicians to stratify patients into groups that would potentially benefit from a meropenem-first vs. colistin-first strategy. Similarly, which strategy has the lowest cost depends significantly on the daily cost of colistin therapy. While colistin is a relatively inexpensive therapy in terms of actual acquisition costs for the medication itself, the sensitivity analyses included a high theoretical daily cost in order to capture potential alternative therapy choices. Some novel antibiotic agents in current or recent development have daily costs running into several hundred dollars per day and poorly-studied side-effect profiles, and the higher range of daily costs is intended to proxy the use of these novel agents in the same role as colistin in this analysis.

In multivariable sensitivity analysis (Figure 6-3), the upper range of probability of encephalopathy from meropenem therapy does make colistin the dominant strategy. However, this high potential rate of encephalopathy comes

from a single reference,[90] is more than triple the rate found in the next highest reference,[91] and likely represents an outlier analysis.

Considerations in the HA scenario differ from the LA scenario since there is a demonstrated mortality benefit to early effective antibiotic therapy in patients with severe infections.[3-9] As such, the ICER for avoided mortality is the major outcome of the HA scenario analysis. Again assuming a 6% prevalence of meropenem resistance, the meropenem-first strategy has lower cost, but higher mortality than the colistin-first strategy, with colistin-first dominating with $46,231 per avoided death, well below any of the tested WTP thresholds. The optimal strategies at different WTP per avoided death as a function of meropenem resistance rate and colistin daily therapy costs are shown in Figures 6-5, 6-6, and 6-7. Below a meropenem resistance rate of ~5.5%, the meropenem-first strategy dominates at any WTP, because mortality is lower in the meropenem-first strategy. This is primarily driven by the increased mortality risk from the higher rates of acute kidney injury observed in the colistin group; with lower rates of acute kidney injury from colistin usage, the colistin-first strategy is favored at lower rates of meropenem resistance. The optimal strategy for HA patients is less sensitive to the costs of colistin therapy than in LA patients since 1) the overall costs of hospitalization for HA patients are substantially higher, and 2) the colistin-first strategy substantially decreases the risk for death in HA patients. While the relative expected costs of the strategies in absolute dollar terms are similar, and thus sensitive to many assumptions made regarding costs an probabilities (Figure 6-4), the preferred strategy in terms of cost-effectiveness is

not sensitive to many of the underlying assumptions, since the colistin-first strategy avoids deaths at little incremental cost.

In both cases, the cost differential between the two strategies is minimal ($2.83 PMPY for the LA scenario and $0.11 PMPY for the HA scenario). By way of comparison, the total PMPY spent is ~$30 for infections, ~$54 for depression, and ~$81 for diabetes.[92]

This analysis looks at costs as incurred by the hospital, rather than amounts paid by insurers or total societal costs. Insurance-payers typically reimburse based on hospital charges as opposed to costs, and while insurance providers rarely pay the full charges, average payments typically exceed hospital-incurred costs. As such, analysis from an insurance-payer perspective would likely substantially increase the costs of both strategies in each scenario. Additionally, we do not consider effects after the initial hospitalization. The rates of rehospitalization and admission to post-acute-care facilities are likely higher for patients with ineffectively treated infections, leading to higher post-discharge costs, which could potentially alter the cost analysis for both scenarios. Higher post-discharge costs for ineffectively treated infections in the LA scenario could cause the colistin-first strategy to be preferable at lower rates of meropenem resistance. Higher post-discharge costs would likely reduce the ICER for the colistin-first strategy in the HA scenario, causing colistin to be favored as a first-line therapy over a wider range of cost/probability combinations.

Our analysis also does not account for the downstream effects of antibiotic overuse. Prior research has demonstrated that use of antibiotics is related to

development of resistance to antibiotics in related classes,[15-19] and prior unpublished research by the authors has demonstrated that exposure to colistin is a risk factor for development of later colistin resistance (Richter 2018, submitted for publication). There may be negative consequences from a colistin-first strategy beyond the hospital costs for the initial visit captured by our model due to development of future colistin resistance. In the HA scenario with a substantial risk for death, these potential future costs are likely not significant compared to the reduction in mortality, but in the LA scenario they may push providers to use colistin only in patients with higher predicted risk for meropenem resistance.

The low acuity scenario analysis relies on the fairly strong assumption that mortality is not a consequence of any decisions made by the provider. While there are strong studies demonstrating that effective empiric antibiotic therapy does not affect mortality in LA patients,[3,66] this assumption is less well-supported for other potential causes of mortality, most significantly the marginal increase in risk of death from acute kidney injury (AKI). Most papers addressing this question attempt some adjustment for baseline patient characteristics and severity of AKI. The range for increase in odds of mortality ranges from 1.0-3.7, with lower odds ratios associated with less sick patients and less severe renal failure.[80-82] Given that the AKI associated with colistin and meropenem administration is typically mild (particularly in LA patients)[90,93,94] and that severity of illness and comorbidities are risk factors for AKI, we felt it was reasonable to assume the lowest end of this range for mortality increase due to AKI in LA patients.

However, if the same calculation were used to determine increased risk for death in LA patients as HA patients (odds ratio of 1.3 multiplied by the initial risk for mortality), this would imply a marginal increase of 2% in risk for death with antibiotic-associated AKI. The marginal increase in mortality for the use of colistin therapy over meropenem therapy would be given by:

[Risk of AKI with colistin (0.14) - Risk of AKI with meropenem (0.04)]*risk of death (0.02)

which yields a 0.2% marginal increase in the risk of death with colistin vs. meropenem therapy. However, since the meropenem-first strategy already costs less than the colistin-first strategy at baseline estimates for the LA scenario, this would reinforce the suggestion for meropenem-first, and (depending on the WTP per avoided death) increase the number of scenarios under which meropenem is favored as the initial antibiotic choice.

Finally, this analysis relies on several assumptions that potentially limit its applicability. By focusing on patients with positive cultures that are useful to guide therapy, we do not directly address patients in whom no organism is recovered. In these patients, therapy is typically guided by symptoms, and at the 72 hour mark patients without clinical improvement (particularly those with severe sepsis or septic shock) will have their antibiotic regimen intensity increased, similarly to the culture-guided strategy we have proposed here. Our analysis only addresses infections with gram-negative organisms. Since empiric therapy for infections typically addresses both gram-positive and gram-negative organisms, the decision for initial empiric gram-negative coverage is relevant to all infections.

In cases in which a gram-positive organism is identified (or in which the patient is determined not to have an infection), gram-negative coverage can be stopped, and the majority of the consequences of this cost-effectiveness analysis will not be applicable.

While this paper applies to undifferentiated gram-negative infections in patients with low or high acuity infections, the general framework can be used to evaluate cost-minimization and cost-effectiveness for a variety of scenarios and antibiotic choices. Further research will focus on infections from specific sources and different initial antibiotic strategies.

Figure 6-1: Simplified Decision Tree

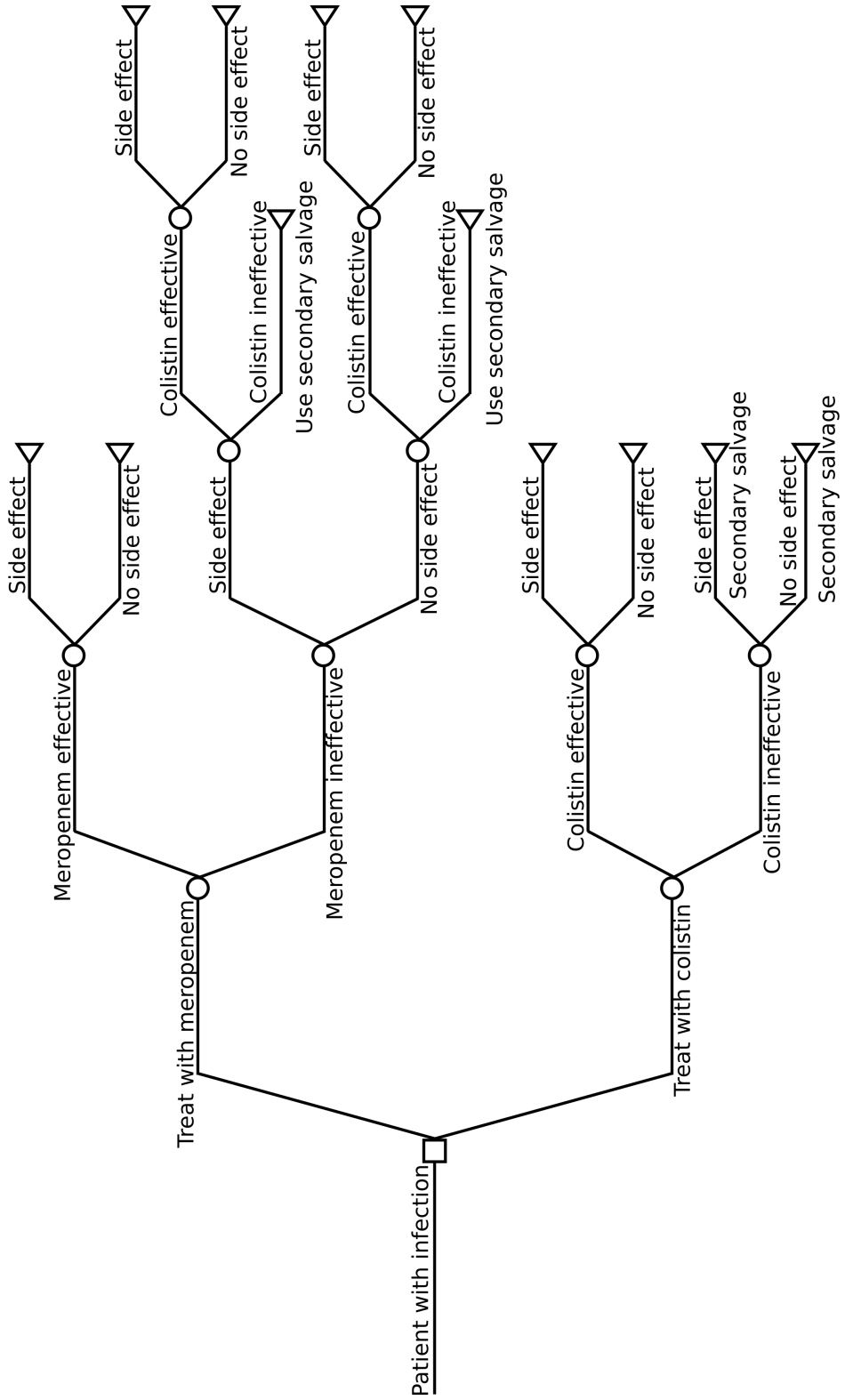

Figure 6-2: Multivariable sensitivity analysis for cost, low acuity patients (Tornado Diagram)

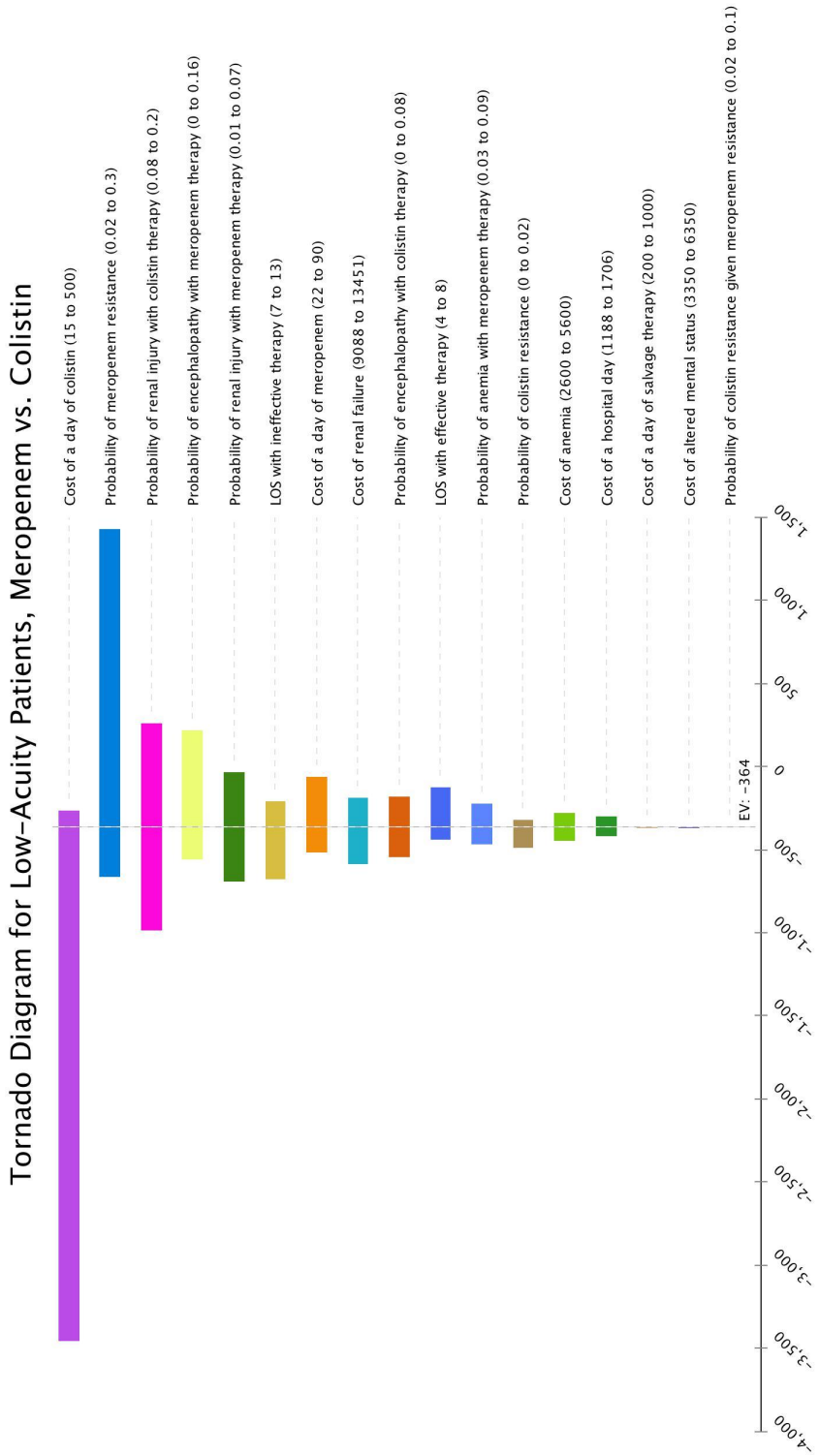

Figure 6-3: Two-way sensitivity analysis for low acuity patients, lowest-cost strategy

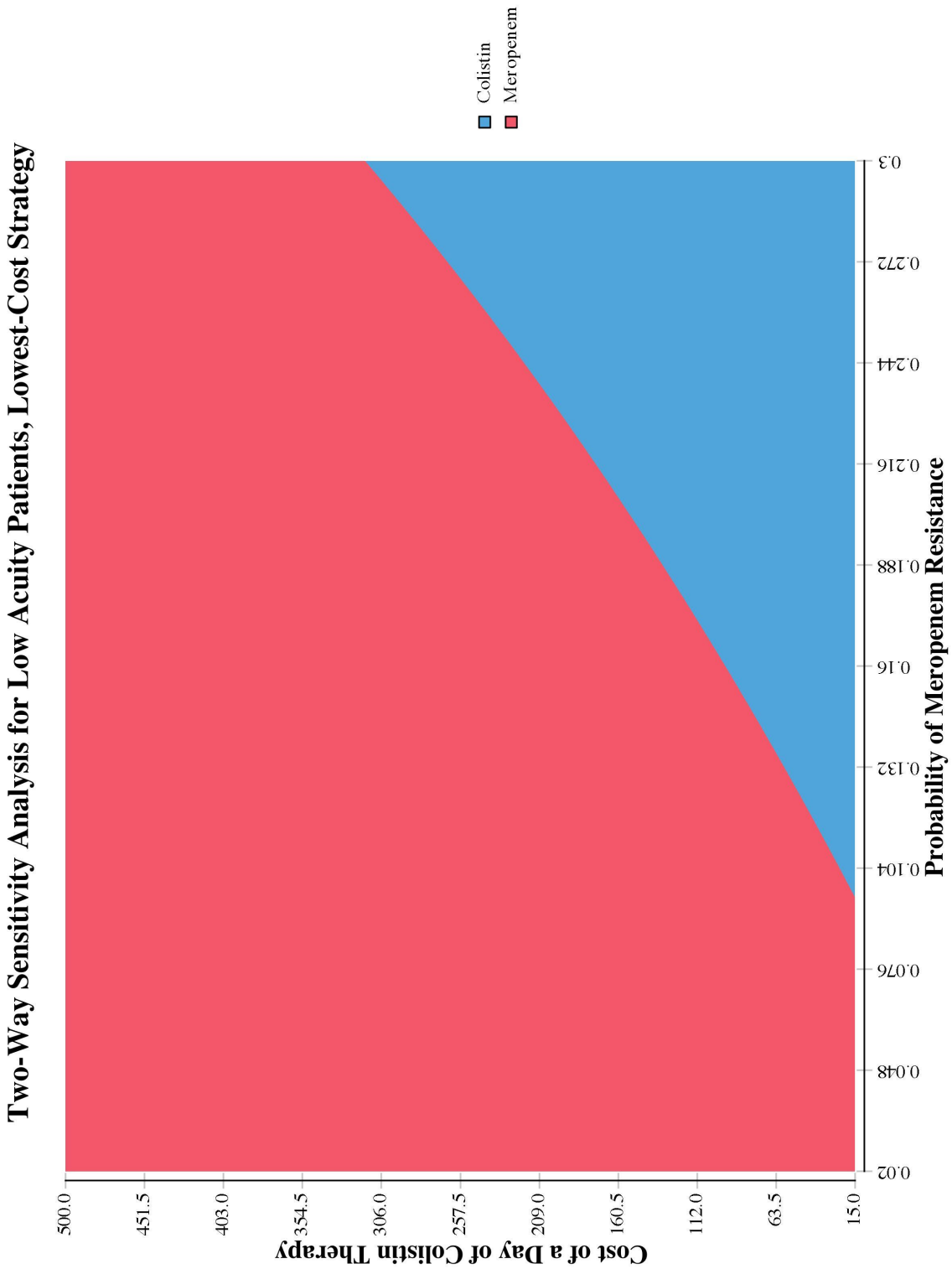

Figure 6-4: Multivariable sensitivity analysis for cost, high acuity patients (Tornado Diagram)

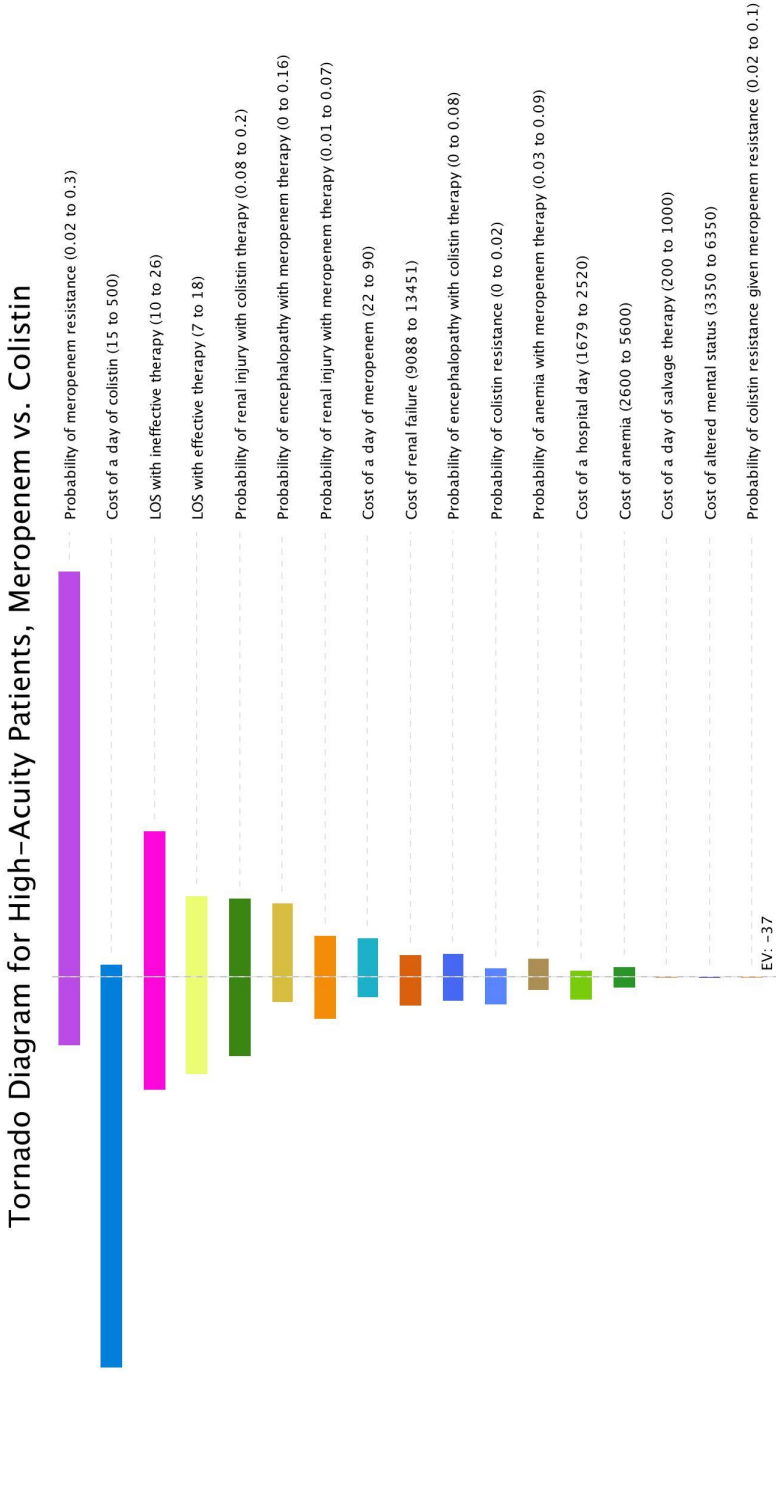

Figure 6-5: Two-way sensitivity analysis for high acuity patients, preferred strategy at willingness-to-pay of $200,000 per avoided death

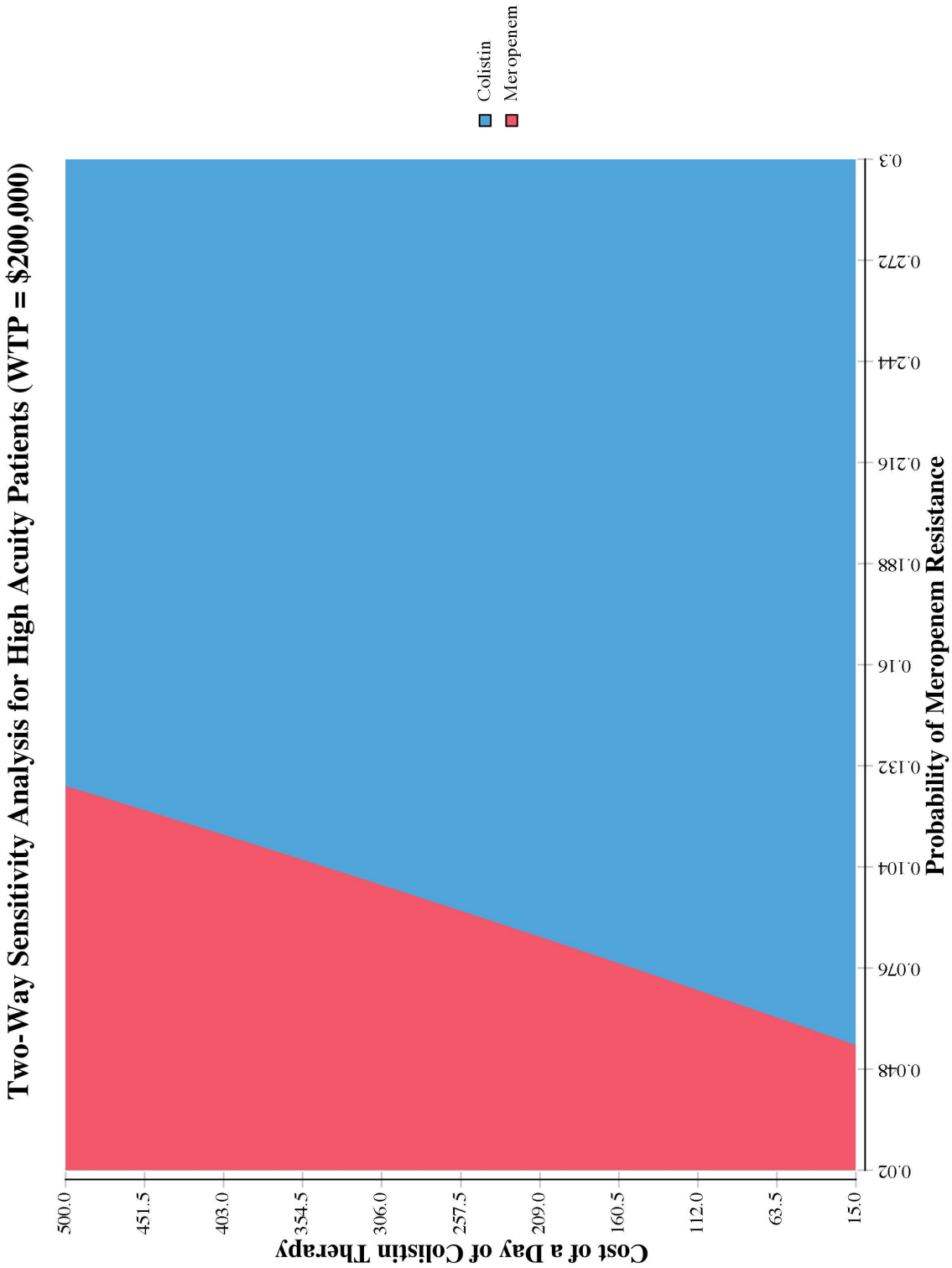

Figure 6-6: Two-way sensitivity analysis for high acuity patients, preferred strategy at willingness-to-pay of $468,750 per avoided death

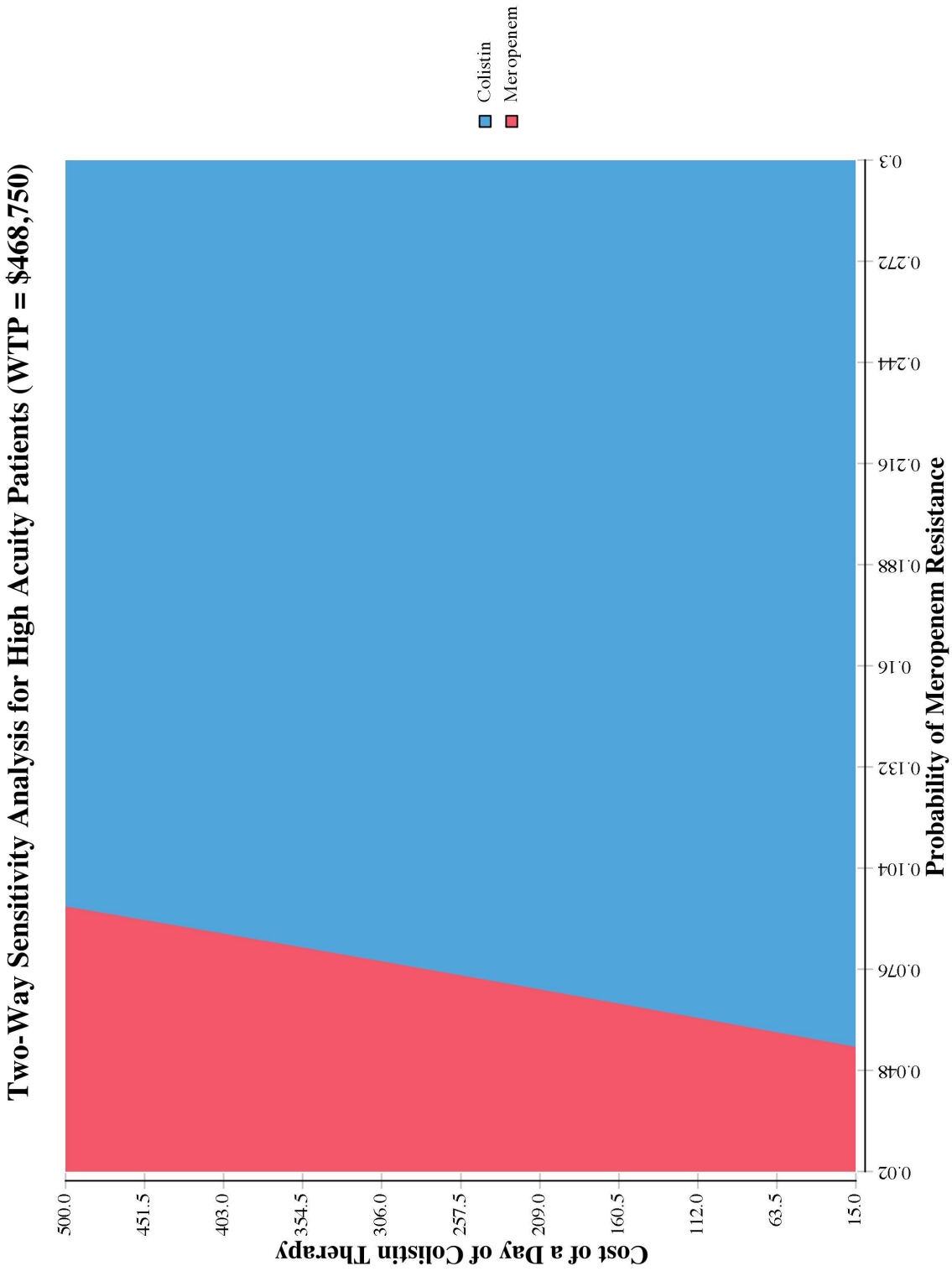

Figure 6-7: Two-way sensitivity analysis for high acuity patients, preferred strategy at willingness-to-pay of $1,250,000 per avoided death

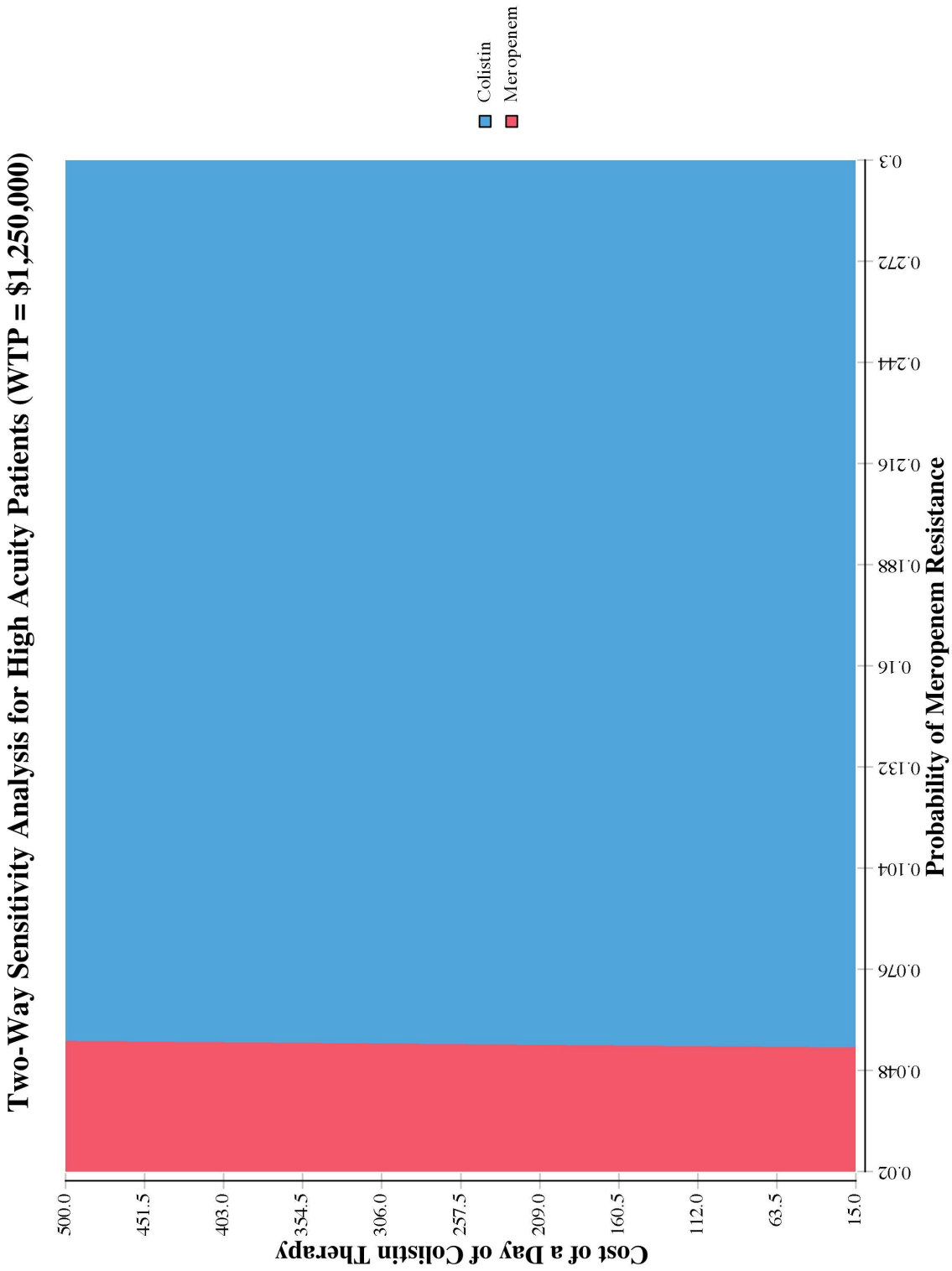

Table 6-1: Base Case Costs, Outcomes, and Probabilities

Costs and Outcomes	Range in Literature	Base Estimate	Justification for base estimate	Range Tested	Justification for range tested	References
Cost for hospital admission for infection	$8,313-$11,945	$10,000	Median value, weighted for infection type	$8,313-$11,945	Range in literature	HCUP 2018[87] Sato 2013[11] Simmering 2017[86] Thaden 2017[95]
Cost for hospital admission for serious infection	$20,147-$30,235	$28,000	Median value, weighted for infection type	$20,147 - $30,235	Range in literature	HCUP 2018[87] Pfuntner 2013[96] Saleh 2010[11] Zilberberg 2017[14]
Length of stay with appropriate therapy for infection	4.2-8 days	7 days	Median value, weighted for infection type	4-8 days	Range in literature	HCUP 2018[87] Lee 2011[85] Restrepo 2008[97] Simmering 2017[86]
Length of stay with inappropriate therapy for infection	Additional 3-5 days	11 days	Median value, weighted for infection type	7-13 days	Tested range plus 3-5 days	Lee 2011[10] Raman 2015[6] Sato 2013[11]
Length of stay with appropriate therapy in sepsis	7-18 days	12 days	Median value, weighted for infection type	7-18 days	Range in literature	HCUP 2018[87] Raman 2015[6] Restrepo 2008[97] Shorr 2011[12] Zilberberg 2017[14]
Length of stay with inappropriate therapy in sepsis	Additional 3-8 days	17 days	Median value, weighted for infection type	10-26 days	Tested range plus 3-8 days	Raman 2015[6] Sato 2013[11] Shorr 2011[12] Tsalik 2016[13] Zilberberg 2017[14]
Cost per day for infection	n/a	$1,429	Cost of hospital stay divided by 7 (expected combined LOS assuming 25% rate of inappropriate initial therapy)	$1,188-$1,706	(Minimum cost)/LOS to (Maximum cost)/LOS	n/a
Cost per day for serious infection	n/a	$2,333	Cost of hospital stay divided by 13.25 (expected combined LOS assuming 25% rate of inappropriate initial therapy)	$1,679-$2,520	(Minimum cost)/LOS to (Maximum cost)/LOS	n/a
QALYs after survival from discharge with sepsis	5.5-7	6.25	Median value	5.5-7	Range in literature	Davies 2005[98] Jones 2011[99] Karlsson 2009[100]
Willingness-to-pay per QALY	$32,000-$200,000	$75,000	Median value	$32K-$200K	Range in literature	Neumann 2015[101] Ryen2015[102] Shiroiwa 2010[103]

Willingness-to-pay per avoided death	n/a	$468,750	(Expected QALYs)*(willingness-to-pay/QALY)	$200K-$1,250K	Expected QALYs*minimum and maximum willingness-to-pay	n/a
Cost per day of meropenem therapy	$45	$45	Actual Acquisition Cost at our institution	$22-$90	Author-determined reasonable range (50-200% of base cost)	UCLA Antibiotic Guide[104]
Cost per day of colistin therapy	$30	$30	Actual Acquisition Cost at our institution	$15-$500	Upper limit includes potential upper costs for novel agents	UCLA Antibiotic Guide[104]
Cost per day of salvage therapy	n/a	$400	Estimate for alternative therapy + complications + ID consult	$200-$1,000	Author-determined reasonable range	n/a
Cost of acute kidney injury	$9,088-$13,451	$11,000	Median value	$9,088-$13,451	Range in literature	Chertow 2005[105] Fuller 2009[79]
Cost of altered mental status	$4,341-$5,389	$4,850	Mean value	$3,350-$6,350	Author-determined reasonable range	Fuller 2009[79]
Cost of anemia	$6,111-$10,296	$4,100	(Mean value)/2 (assuming 50% risk for transfusion with drug-induced anemia)	$2,600-$5,600	Author-determined reasonable range	Fuller 2009[79]
Probabilities	Range in Literature	Probability Used	Justification for base estimate	Range Tested	Justification for range tested	References
Probability of meropenem resistance	4.5-6%	6%	Available data	0-30%	Limits of scoring system	Richter 2018 (unpublished) Cai 2017[89]
Probability of colistin resistance	0.5%	0.5%	Available data	0-2%	Colistin resistance is rare, but increasing; chosen based on possible future rates	Richter 2018 (unpublished)
Probability of colistin resistance | meropenem resistance	5.2%	5.2%	Available data	2-10%	Colistin resistance is rare, but increasing; chosen based on possible future rates	Richter 2018 (unpublished)
In-hospital mortality with appropriate therapy for infection	4-18%	6%	Weighted for type of infection	n/a	Range in literature	Gradel 2017[3] Restrepo 2008[97] Thom 2008[66]
In-hospital mortality with inappropriate	No change	6%	Per literature	n/a	Range in literature	Gradel 2017[3] Thom 2008[66]

therapy for infection						
In-hospital mortality with appropriate therapy for serious infection	15-28%	22%	Weighted for type of infection	15-28%	Range in literature	Gradel 2017[3] Kohler 2017[4] Paul 2010[5] Raman 2015[6] Restrepo 2008[97] Retamar 2012[7]
In-hospital mortality with inappropriate therapy for serious infection	1.2-3.0 OR increase	35.20%	Used 1.6 OR, median value and best evidence	28-45%	1.6 times upper and lower limits	Gradel 2017[3] Kohler 2017[4] Paul 2010[5] Raman 2015[6] Retamar 2012[7]
Risk of renal impairment with meropenem	1-7%	4%	Middle of range	1-7%	Range in literature	Imani 2017[90] Meropenem Package Insert[106]
Risk of renal impairment with colistin	8-20%	14%	Middle of range	8-20%	Range in literature	Falagas 2005[93] Kasiakou 2005[107] Michalopoulos 2010[108] Pintado 2008[94]
Risk of neurotoxicity with meropenem	0-16%	4%	Median value	0-16%	Range in literature	Imani 2017[90] Joseph 2008[109] McDonald 2016 [91] Meropenem Package Insert[106]
Risk of neurotoxicity with colistin	0-8%	4%	Middle of range	0-8%	Range in literature	Falagas 2005[93] Kasiakou 2005[107] Michalopoulos 2010[108]
Risk of anemia with meropenem	5.5%	5.5%	One source	3-9%	Author-determined reasonable range	Meropenem Package Insert[106]
Marginal increase in risk of death with renal impairment	1.0-3.7 OR increase	7%	(OR from most applicable study)*(base case for appropriately -treated infection)	0-15%	Author-determined reasonable range	Iwagami 2016[80] Jurawan 2017[81] Wang 2012[82]
Marginal increase in risk of death with delirium	1.0-2.2 OR increase	0%	Most applicable study found no increased risk once controlling for other factors	0-5%	Author-determined reasonable range	Salluh 2015[110] van den Boorgaard 2010[83]
Marginal increase in risk of death with anemia	n/a	0%	Unable to find applicable studies	0-5%	Author-determined reasonable range	n/a

Chapter 7 - Limitations and Conclusions

Project 1

The papers in the first project suffer from two primary limitations, both stemming from the nature of the data. The first limitation comes from the incompleteness of the data; the models are built off of only what is available from the xDR data repository. Since data are only available from inpatient stays in which a patient had a positive blood culture, there is no information available regarding outpatient treatment, either at UCLA or other facilities, or hospitalizations at other facilities. Exposure to antibiotics and resistant infections are constructs that are central to the model and are incompletely captured by the dataset. As such, many of the measures that appear frequently in the models (e.g. admission from an outside facility, some measures of chronic medical illness/comorbidities, and presence of indwelling devices) may owe a large amount of their predictive power to their ability to proxy for these unmeasured exposures. Additionally, some measures are incomplete. Perhaps the most important incomplete field is the in_facility variable denoting whether a patient was admitted from an outpatient medical facility. These data are taken from the patient's social history section of the medical chart, and must be entered by hand by the receiving nurse; it is likely that human error or expediency is responsible for incomplete information. Additionally, this variable does not capture patients who were discharged from a facility back to their communities/homes, and then admitted back to UCLA shortly thereafter (within a day, week, or month), which is potentially a very common occurrence in patients with chronic medical disease.

However, since the goal of the scoring systems is to create a score that can be calculated using available data (and hopefully eventually automated), the shortcomings of this dataset reasonably approximate the limitations physicians encounter on a daily basis when attempting to make clinical decisions with incomplete information.

The second significant potential limitation of the first project is its external validity. Since all of the data come from a single institution, it is possible that these models are not applicable to other medical systems. The work described has several safeguards that mitigate this effect. First, the dataset draws from two hospitals that serve somewhat different populations. Ronald Reagan Medical Center has a high proportion of patients undergoing transplants of either solid organs or bone marrow, a robust neurosurgery patient population, and a large number of patients with chronic severe medical illness. Santa Monica UCLA is a community hospital with a focus on geriatrics, orthopedic procedures, and solid oncology patients. Second, the dataset contains tens of thousands of patients, one to two orders of magnitude larger than other similar studies examining risk factors for infection with resistant organisms. Third, as shown above, the bivariate predictor variables largely match up with predictors described in previous work. Finally, in order to prevent overfitting, the final models were restricted to a small number of predictor variables. Nevertheless, external validity is always a concern for single-institution studies, and further work will focus on validating these prediction scores on more diverse datasets.

Project 2

Potential weaknesses of the second project stem primarily from the assumptions made to facilitate model interpretability. Several of the assumptions - that duplicate complications from two separate medications do not add to cost or mortality risk, that patients will be treated with seven days of effective therapy, and that complications happen within the first 72 hours - do not have substantial effects on the outcomes (data not shown). Additionally, the assumption that there is a single “secondary salvage” regimen in the case of colistin non-susceptibility with fixed daily costs does not have a significant effect on outcomes, as shown in the multivariable sensitivity analyses demonstrating that the cost and nature of secondary salvage has little influence on the costs of the different strategies.

Some assumptions have a possibility of affecting the outcome. Complications from antibiotic therapy are calculated as adding a flat cost (as opposed to increased length of stay); this cost is identical in the high and low acuity groups, which probably does not directly reflect reality. The cost of some of these complications, most notably renal failure, do exert some potentially significant influence on the optimal strategy in the low acuity scenario, and would likely change the optimal strategy across some of the relevant range of meropenem resistance rates if it were inappropriately calculated. The assumption that the expected cost of a hospitalization resulting in death is identical to that of one resulting in discharge is potentially significant, and could affect the calculations in the high acuity scenario. Currently, the data do not exist in the literature in a convincing form to allow for differentiation of the two scenarios.

Additionally, the optimally cost-effective strategy in the high acuity scenario was shown to be relatively insensitive to most factors related to cost (and, in fact, to most things besides rates of meropenem resistance).

Perhaps the most significant assumption in the analysis is that patients would present with only Gram-negative infections, thus ignoring the possibility of Gram-positive, fungal, or anaerobic infections. This assumption was made to guide the analysis towards answering a specific question, but it does require the results to be modified to apply to more realistic situations. However, this modification is relatively minor - divide the expected rate of meropenem resistance among Gram-negatives by the local prevalence of Gram-negative infections as a fraction of total infections. For example, if at a given hospital 50% of all infections were caused by Gram-negative bacteria, the threshold values for switching from meropenem to colistin as an initial strategy would be twice those described in the paper above.

Conclusions

How measures relate to outcomes

The models developed in the first three papers of the thesis expand on work previously done on similar topics, using larger datasets and more complete measures. They additionally each provide actionable results in the form of scoring systems that could guide clinical therapy, particularly in conjunction with cost-effectiveness analyses such as those presented in the second project. Due to the large sample size relative to prior papers (the work of this thesis draws from tens of thousands of samples, while prior research typically has sample sizes in the hundreds to thousands), significantly more predictive factors were found to be statistically significant on univariate analysis. On multivariable analysis, many of these predictors are collinear and serve to proxy similar constructs, as detailed above in the conceptual model. The following is a review of the contributions of various types of data elements and their contributions across models.

Demographic information - age, gender, race, social history

Demographic information was generally of minimal importance to the final models, with the exception of male gender, which figured prominently in the prediction of resistance to amikacin and both classes of carbapenems. That age was not a prominent predictor at almost any stage of the model construction was somewhat surprising, as older age is a strong risk factor for almost all medical comorbidity; it is likely that medical comorbidities more accurately captured the variance associated with age, as they are the primary mediator for the influence

of age on outcome. That gender remains a significant risk factor for several types of antibiotic resistance even when controlling for medical comorbidities suggests that gender may have influence on the outcome that is not fully mediated by chronic medical illness. This could potentially be through unexplored pathways such as higher-risk behavior leading to more frequent contact with the medical system, more frequent exposure to infection with high-risk or already-resistant bacteria, or it is possible that men receive antibiotics at a higher rate than women.

Location prior to admission

This was the most consistent predictor of resistance across the predictive models, likely because it represents several key constructs in the conceptual model. Residence in a long-term medical facility prior to transfer is most directly associated with frequent contact with the medical system, but it also implies a degree of significant chronic medical illness. Additionally, most long-term medical facilities have high rates of resistant bacteria, increasing the risk of exposure to high-risk and already-resistant bacteria. The models could likely be substantially improved by obtaining more complete information regarding the amount of exposure to long-term medical facilities, since the data field in CareConnect from which this information is drawn does not account for residence in these facilities that does not take place immediately prior to transfer.

Location within the hospital - in ICU vs. regular medical floor

While patient location in an ICU (either currently or previously during the index hospitalization) was associated in most cases with a higher likelihood of

resistance, its effect on the outcome was in all cases better explained by other variables, typically the presence of a tracheostomy or ventilator. Since ventilators can only be administered within an ICU and patients are admitted to the ICU for other reasons, it appears likely that the presence of the indwelling device, rather than the absolute level of acute medical illness, is associated with risk for antibiotic resistance. Admission to an ICU is a marker of acute illness that is correlated with chronic medical illness; its association with chronic medical illness (and thus the outcome) is likely better proxied by other variables, and acute medical illness does not appear to have a direct effect on the final outcome.

Medical comorbidities - Elixhauser index

Chronic medical comorbidities are the best proxy available in the dataset for chronic medical illness, which is upstream of almost all of the major constructs in the conceptual model. However, specific comorbidities are present in only about half of the studied models, likely because the effects of chronic medical illness are mediated by a variety of constructs for which we have reasonable proxies. The medical comorbidities that are present in the final stages of the models are typically neurologic disease, weight loss, and cystic fibrosis. Neurologic disease and weight loss, while related to specific diagnostic codes, can be indicators of global dysfunction, and can serve as a proxy for general overall debility, which leads to increased susceptibility to infection. Cystic fibrosis is a specific genetic condition that leads directly to respiratory colonization with high-risk species and persistent exposure to antibiotics as a regular part of treatment, as well as increased susceptibility to infection due to impaired airway clearance. Since

many of the multi-drug resistant infections studied are predominantly respiratory in nature, the role of cystic fibrosis as a risk factor is not particularly surprising.

Laboratory values and vital signs

While there were multiple laboratory values and vital signs that were associated with the outcomes of interest on univariate analysis, in most cases neither of these categories had significant contributions to the overall risk for antibiotic resistant infections. These two sets of variables primarily are associated with acute illness, and relate to the model as proxies for chronic medical illness (in that chronic medical illness increases a patient's risk for acute medical illness). Predictably, this is better proxied by other variables in the model, specifically medical comorbidities and indwelling devices. A notable exception to this is hemoglobin - anemia (represented by hemoglobin <11) was present in several final models. This is likely because chronic anemia can be a marker of overall medical comorbidity (much like weight loss), and serves as a reasonable proxy for chronic medical illness in some situations.

Indwelling devices - tracheostomies, ventilators, and indwelling urinary catheters

While indwelling urinary catheters were associated with the outcome in most cases, variables associated with indwelling ventilatory devices were more likely to end up in the final models. The exact variable - current tracheostomy, ever tracheostomy, current ventilation, or ever ventilation - varies depending on the model, but in general ventilatory support is associated strongly with the primary outcome. This is likely because persistent ventilatory support proxies not only chronic medical illness, but frequently necessitates frequent contact with the

medical system (usually through long-term medical facility residence) and directly increases susceptibility to infection via bypassing natural host defenses.

Medications received

While many classes of medications were associated with infection with resistant bacteria on univariate analysis, only recent antibiotic usage was included in the final multivariable models. This is likely because non-antibiotic medications serve as proxies for chronic medical illness, which is better represented by other variables. Recent antibiotic usage proxies for several important predictive constructs. First, it directly informs prior exposure to antibiotics, which is potentially directly mechanistically related to the development of de novo resistance mutations, an important final pathway to the outcome of interest. Second, recent exposure to antibiotics is indicative of prior infections, which are relevant in both final pathways to infection with resistant bacteria. Third, broad-spectrum antibiotics are preferentially administered to patients who are chronically ill and in frequent contact with the medical system, and this may proxy some of that construct that is not fully explained by the medical record. In all cases, the amount of time since last receipt of a carbapenem was significantly associated with the outcome on multivariable analysis. Additionally, time since last receipt of an anti-MRSA agent was a significant predictor in three of the six models. Since it is unlikely that anti-MRSA agents (or carbapenems, for non-carbapenem-related outcomes) directly lead to antibiotic resistance, time since receipt of these antibiotic classes is most likely serving as a proxy for recent infections and contact with the medical system.

Low- vs. high-level resistance

The discriminatory power of the models predicting higher-level resistance (corresponding to more difficult-to-treat infections) was substantially greater than those predicting lower-level resistance. The model predicting ertapenem resistance had an AUROC of 0.684 compared to 0.754 for predicting resistance to anti-pseudomonal carbapenems; the model predicting gentamicin/tobramycin resistance had an AUROC of 0.634 compared to 0.735 for predicting resistance to amikacin. The discriminatory power of the colistin models (0.808 for gram negative rods and 0.887 for *Klebsiella pneumoniae*) are higher than for the other antibiotic classes. This is most likely because development of high-level resistance is a less random event than development of low-level resistance. Ertapenem and gentamicin/tobramycin are considered less powerful antibiotics than anti-pseudomonal carbapenems and amikacin, respectively, because resistance to them is more common. Organisms with low-level resistance are easier to acquire outside of the pathways described in the model, while organisms with high-level resistance exist more preferentially in healthcare settings and as a result of de novo mutations, as such, patients with infections with low-level resistance more closely resemble patients without resistance.

Correlated Resistance

There is significant overlap between the risk factors for resistance to the various antibiotics studied in Project 1, particularly for high-level resistance.

While the final multivariate models have different specifications, the bivariate correlations are similar across the antibiotics. Additionally, several recurrent factors (most notably neurologic disease, weight loss, hemoglobin, several indwelling devices, male gender, transfer from an outside facility, and recent administration of various antibiotic classes) can be seen in the model selection process, even if they did not make it into the final models (see Appendices A, B, and C). This implies that there is likely a fair amount of correlation between resistance to all of the studied antibiotics, and that organisms with high probability of resistance to one antibiotic are likely at high risk for resistance to other antibiotics. This was explicitly studied in Chapter 3, where prior carbapenem resistance is seen as a major risk factor in the final models predicting colistin resistance in both GNRs and *K. Pneumoniae*.

The work of this thesis does not specifically address the question of choices among antibiotic classes, and this is a major direction for future study. There are likely subtle differences in the risk patterns between various antibiotic classes, and identification of these differences will be necessary to address the question of optimal empiric antibiotic strategy in these cases. Further research will focus on risk factors that allow differentiation of the various resistance patterns and prediction of the optimal initial antibiotic for empiric therapy. Another possible strategy would involve switching to a combination of other antibiotics once there is a sufficiently high probability of resistance to a given antibiotic (for example, using a combination of amikacin and a fluoroquinolone to treat

infections with a high risk for anti-Pseudomonal carbapenem resistance). Future work will also focus on the cost-effectiveness of such strategies.

Cost-effectiveness analysis

A key conclusion from the second project is that the pre-test probability of meropenem resistance should be an important factor in decisions regarding initial choice of antibiotics in both the low and high acuity scenarios. The range of meropenem non-susceptibility for the cost-effectiveness paper was chosen to mirror the range demonstrated by the score from the second paper, from 0-30%. In the context of the cost-effectiveness analysis, the meropenem resistance rate was shown to influence the optimal strategy for the low acuity scenario across the entirety of this range, while for the high acuity scenario the relevant range (across several willingness-to-pay thresholds) was from approximately 5-12%. This demonstrates the utility of the advanced carbapenem resistance prediction score, particularly in the high acuity scenario. For high acuity patients with a score of 0 or 1, initial therapy with meropenem is a strictly dominant strategy (lower cost and lower likelihood of death). Similarly, for patients with a score of 3 or higher, initial therapy with colistin is a strictly dominant strategy.

Further research for cost-effectiveness analysis will focus on specific types of infection (urinary tract, bloodstream, and respiratory) and different antibiotic combinations, attempting to apply the scores developed in the other papers and to examine the tradeoffs in situations in which the infection source is known.

Appendix A - Model selection for colistin resistance

Table A-1: Model selection for colistin resistance in GNRs, comorbidities and demographics

	Comorbidities - start	Comorbidities - end	Comorbidities + demographics - end
AUROC	0.707	0.686	0.746
Variable			
elixhauser_score	-0.029*	-0.019*	
arrhythmia	0.511*	0.552**	
neurologic_dz	1.190***	1.225***	0.791**
renal_dz	0.116		
tumor_without_mets	-0.480		
weight_loss	0.545*	0.519*	
electrolyte_disorders	0.315		
renal_failure	0.427		
cystic_fibrosis	1.447***	1.421***	1.714***
in_facility			1.509***
male			0.546*
_cons	-6.065***	-6.010***	-6.36***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant comorbidities

- Dropped all comorbidities that did not remain significant on multivariable analysis

- Added in demographic variables (age, gender, race, location prior to admission, etc.)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table A-2: Model selection for colistin resistance in GNRs, labs and devices

	Labs - start	Labs - end	Labs + devices
AUROC	0.660	0.648	0.715
Variable			
neutrophil	0.009		
monocyte	-0.004		
eosinophil	0.508***	0.545***	0.488*
basophil	0.428		
hemoglobin	-0.223***	-0.226***	-0.095
ever_vented			1.314***
_cons	-3.427***	-3.290***	-5.174***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant laboratory values

- Tried combinations of lab values until parsimony was achieved. Neutrophils, monocytes, eosinophils, and basophils are all types of white blood cells; best represented by eosinophils

- Added in information about indwelling devices (tracheostomy, urinary catheter, ventilator)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC). Removing hemoglobin significantly dropped the AUROC (to 0.684) despite not being significant

Table A-3: Model selection for colistin resistance in GNRs, combining comorbidities, demographics, labs, and devices together

	Combined model, start	Combined model, end
AUROC	0.816	0.780
Variable		
eosinophil	0.383	
hemoglobin	-0.119	
ever_vented	1.062***	1.217***
neurologic_dz	0.455	0.567*
cystic_fibrosis	1.944***	1.693**
in_facility	1.481***	1.488***
male	0.366	
_cons	-5.758***	-6.539***

p-values: * <0.05, ** <0.01, *** <0.001

- Combined end model from labs + devices with end model from comorbidities + demographics

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table A-4: Model selection for colistin resistance in GNRs, recent medications plus above variables

	Recent therapy	Recent therapy + other constructs	Final model
AUROC	0.754	0.817	0.801
Variable			
ever_vented		0.766**	0.646*
neurologic_dz		0.407	0.440
cystic_fibrosis		1.069	
in_facility		1.369***	1.220***
prior_carb_resist	0.937***	0.412	0.771**
last_ertamero	-0.006*	-0.007*	-0.009**
last_polymyxin	-0.007*	-0.005	
last_anti_GPC	-0.009**	-0.004	
_cons	-4.173***	-5.248***	-5.602***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant recent medications (and prior carbapenem resistance)

- Unable to drop any recent medications without significantly affecting AUROC

- Added in variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table A-5: Model selection for colistin resistance in GNRs, simplified final model

	Final model - simplified
AUROC	0.808
Variable	
advanced_O2	0.645*
neurologic_dz	0.498*
in_facility	1.247***
prior_carb_resist	0.721**
carb90	0.959***
_cons	-6.510***

p-values: * <0.05, ** <0.01, *** <0.001

- Dichotomized “last_ertamero” to whether or not carbapenems were received in the prior 90 days for simplicity of interpretation, after testing multiple thresholds for time cutoffs (30, 60, 90 days) and determining that 90 days had the best discriminatory capacity for the model

Table A-6: Model selection for colistin resistance in *Klebsiella pneumoniae*, comorbidities and demographics

	Comorbidities - start	Comorbidities - end	Comorbidities/demographics - end
AUROC	0.731	0.723	0.779
Variable			
elixhauser_score	-0.037*		
renal_failure	0.574*	0.423	
arrhythmia	0.761**	0.513*	
neurologic_dz	1.500***	1.317***	1.060***
weight_loss	0.657*		
electrolyte_disorders	0.253		
male			0.541
in_faciility			1.976***
_cons	-5.046***	-5.193***	-5.552***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant comorbidities

- Dropped all comorbidities that did not remain significant on multivariable analysis

- Attempted to further drop comorbidities until parsimony was achieved (dropping renal failure reduced AUROC to 0.709 despite not being significant)

- Added in demographic variables (age, gender, race, location prior to admission, etc.)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table A-7: Model selection for colistin resistance in *Klebsiella pneumoniae*, labs and devices

	Labs - start	Labs - end	Combined model
AUROC	0.705	0.701	0.814
Variable			
neutrophil	0.009	0.015	
eosinophil	0.544**	0.527**	
basophil	2.126		
hemoglobin	-0.162*	-0.219**	-0.243*
GFR	-0.005		
ALK	0.001*		
creatinine	-0.006		
anion_gap	0.019		
neurologic_dz			0.993**
in_facility			2.071***
_cons	-2.985**	-2.367***	-2.951***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant laboratory values

- Tried combinations of lab values until parsimony was achieved. Neutrophils, monocytes, eosinophils, and basophils are all types of white blood cells; best represented by neutrophils and eosinophils

- Added in information about indwelling devices (tracheostomy, urinary catheter, ventilator) - none significantly improved the model; this step is not shown

- Added variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC).

Table A-8: Model selection for colistin resistance in *Klebsiella pneumoniae*, recent medications plus above variables

	Recent therapy - start	Recent therapy + other constructs	Final model
AUROC	0.786	0.874	0.902
Variable			
hemoglobin		-1.430	
neurologic_dz		2.470*	0.750*
in_facility		5.900***	2.003***
last_carbapenem	-0.004	-2.910**	-0.009
last_anti_GPC	-0.015**	-2.380*	-0.013*
last_polymyxin	-0.016***		
last_probiotic	-0.011**		
prior_carb_resist			1.622***
_cons	-0.967	-2.380*	-4.688***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant recent medications

- Unable to drop any recent medications without significantly affecting AUROC

- Added in variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in prior carbapenem resistance, repeated parsimony step

- As a double-check, performed the same analysis adding in prior carbapenem resistance at earlier stages of the model, ended with the same final model

Table A-9: Model selection for colistin resistance in *Klebsiella pneumoniae*, simplified final model

	Final model - simplified
AUROC	0.887
Variable	
neurologic_dz	0.748*
in_facility	1.888***
carb90	0.764
GPC90	1.167*
prior_carb_resist	1.575***
_cons	-6.760***

p-values: * <0.05, ** <0.01, *** <0.001

- Dichotomized “last_carbapenem” and “last_anti_GPC” to whether or not these antibiotics were received in the prior 90 days for simplicity of interpretation, after testing multiple thresholds for time cutoffs (30, 60, 90 days) and determining that 90 days had the best discriminatory capacity for the model

Appendix B - Model selection for carbapenem resistance

Table B-1: Model selection for ertapenem resistance in GNRs, comorbidities and demographics

	Comorbidities - start	Comorbidities - end	Comorbidities + demographics - start	Comorbidities + demographics - end
AUROC	0.601	0.600	0.600	0.638
Variable				
CHF	-0.014			
arrhythmia	0.111**	0.122***	0.103	
valve_disease	-0.034			
pulm_vasc_dz	0.038			
peripheral_vasc_dz	0.078*			
paralysis	0.123*			
neurologic_dz	0.38***	0.390***	0.112	
chronic_pulm_dz	0.272***	0.282***	0.221***	0.213***
renal_dz	0.017			
liver_dz	-0.186***			
coagulopathy	0.029			
weight_loss	0.390***	0.379***	0.317***	0.359***
electrolyte_disorders	0.005			
renal_failure	0.188***	0.155***	0.146	
bmi			-0.009*	
age			-0.006***	
male			0.511***	0.550***
in_facility			0.596***	0.563***
ever_icu			0.485***	0.551***
_cons	-1.438***	-1.445***	-1.531***	-2.062***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant comorbidities

- Dropped all comorbidities that did not remain significant on multivariable analysis

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in demographic variables (age, gender, race, location prior to admission, etc.)
- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table B-2: Model selection for ertapenem resistance in GNRs, comorbidities, demographics, and devices

	Comorbidities/demographics + devices - start	Comorbidities/demographics + devices - end
AUROC	0.675	0.666
Variable		
chronic_pulm_dz	-0.019	
weight_loss	0.224	
male	0.918***	0.883***
in_facility	0.031	
ever_icu	0.134	
urine_cath	0.468***	0.512***
trach	0.446	0.526*
ever_vented	0.431*	0.486***
_cons	-2.782***	-2.794***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of comorbidities/demographics from above, added significant indwelling devices

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC).

Table B-3: Model selection for ertapenem resistance in GNRs, combining comorbidities, demographics, devices, and labs together

	Labs - start	Labs - end	Labs + above
AUROC	0.624	0.604	0.670
Variable			
WBC	0.010***	0.012***	
hemoglobin	-0.117***	-0.125***	-0.078***
platelets	0.001***		
sodium	-0.025***		
potassium	0.054		
chloride	0.029***		
bicarb	0.068***	0.052***	
GFR	0.006***		
BUN	0.010***		
glucose	-0.001**		
ever_vented			0.521***
trach			0.835***
male			0.439***
_cons	-2.210***	-1.290***	-1.096***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with significant labs

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in end model from above (comorbidities, demographics, and indwelling devices)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table B-4: Model selection for ertapenem resistance in GNRs, recent medications plus above variables

	Recent therapy - start	Recent therapy - end	Final model
AUROC	0.645	0.641	0.681
Variable			
last_abx	0.000		
last_carbapenem	-0.007***	-0.007***	-0.006***
last_fluoroquin	-0.001*		
last_anti_GPC	-0.007***	-0.007***	-0.006***
last_betalactam	-0.001		
last_antacid	-0.003***	-0.003***	
last_probiotic	-0.004***	-0.004***	
last_chemo	-0.002		
last_blood	0.000		
male			0.338***
ever_vented			0.398***
trach			0.703***
_cons	0.359*	0.130	-0.964***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant recent medications

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table B-5: Model selection for ertapenem resistance in GNRs, simplified final model

	Final model - simplified
AUROC	0.684
Variable	
carb30	0.600***
GPC30	0.488***
male	0.365***
ever_vented	0.404***
trach	0.703***
_cons	-2.113***

p-values: * <0.05, ** <0.01, *** <0.001

- Dichotomized “last_carbapenem” and “last_anti_GPC” to whether or not antibiotics were received in the prior 30 days for simplicity of interpretation, after testing multiple thresholds for time cutoffs (30, 60, 90 days) and determining that 30 days had the best discriminatory capacity for the model

Table B-6: Model selection for anti-pseudomonal carbapenem resistance in GNRs, comorbidities and demographics

	Comorbidities - start	Comorbidities - end	Comorbidities + demographics - start	Comorbidities + demographics - end
AUROC	0.632	0.628	0.707	0.638
Variable	Significance	Significance	Significance	Significance
CHF	0.176**			
arrhythmia	0.262***	0.283***	0.213**	0.279***
valve_disease	-0.215***			
pulm_vasc_dz	-0.004			
peripheral_vasc_dz	-0.051			
paralysis	0.082			
neurologic_dz	0.444***	0.467***	0.080	
chronic_pulm_dz	0.214***	0.203***	0.152	
renal_dz	-0.064			
liver_dz	-0.076			
coagulopathy	0.174**	0.192***	0.188*	
weight_loss	0.471***	0.488***	0.394***	0.445***
electrolyte_disorders	0.158**			
renal_failure	0.201**			
age			-0.007***	-0.007***
male			0.542***	0.538***
in_facility			1.119***	1.121***
ever_icu			0.668***	0.692***
_cons	-3.318***	-3.270***	-3.431***	-3.345***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant comorbidities

- Dropped all comorbidities that did not remain significant on multivariable analysis

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in demographic variables (age, gender, race, location prior to admission, etc.)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table B-7: Model selection for anti-pseudomonal carbapenem resistance in GNRs, comorbidities, demographics, and devices

	Comorbidities/demographics + devices - start	Comorbidities/demographics + devices - end
AUROC	0.766	0.763
Variable		
arrhythmia	0.303	
weight_loss	0.096	
age	-0.003	
male	0.997***	1.045***
in_facility	0.654**	0.669**
ever_icu	0.173	
urine_cath	0.403	0.412*
ever_vented	0.982***	1.173***
admission_trach	0.092	
_cons	-4.614***	-4.67***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of comorbidities/demographics from above, added significant indwelling devices

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC).

Table B-8: Model selection for anti-pseudomonal carbapenem resistance in GNRs, combining comorbidities, demographics, devices, and labs together

	Labs - start	Labs - end	Labs + Above
AUROC	0.653	0.645	0.773
Variable			
WBC	0.008***		
hemoglobin	-0.178***	-0.175***	-0.132**
platelets	0.001***		
sodium	0.023**		
potassium	0.069		
chloride	-0.002		
bicarb	0.044***	0.050***	
GFR	0.006***	0.007***	
BUN	0.010***	0.012***	
glucose	-0.001		
male			1.012***
in_facility			0.695***
urine_cath			0.392
ever_vented			1.003***
_cons			-3.269***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with significant labs

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in end model from above (comorbidities, demographics, and indwelling devices)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC). Urine cath could not be dropped, despite not being significant.

Table B-9: Model selection for anti-pseudomonal carbapenem resistance in GNRs, recent medications plus above variables

	Recent therapy - start	Recent therapy - end	Final model
AUROC	0.716	0.723	0.757
Variable			
last_abx	-0.002		
last_carbapenem	-0.011***	-0.013***	-0.014***
last_fluoroquin	-0.003***		
last_anti_GPC	-0.008***	-0.008***	
last_betalactam	0.000		
last_antacid	-0.004***	-0.004***	
last_probiotic	-0.007***	-0.007***	
last_chemo	-0.001		
last_blood	0.000		
male			0.411***
in_facility			0.985***
ever_vented			0.728***
hemoglobin			-0.071***
_cons	-0.419*	-0.689***	-1.812***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant recent medications

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table B-10: Model selection for anti-pseudomonal carbapenem resistance in GNRs, simplified final model

Final model - simplified	Final model - simplified
AUROC	0.754
Variable	
carb30	1.207***
male	0.432***
in_facility	0.967***
ever_vented	0.753***
hem11	-0.377***
_cons	-3.717***

p-values: * <0.05, ** <0.01, *** <0.001

- Dichotomized “last_carbapenem” to whether or not carbapenems were received in the prior 30 days for simplicity of interpretation, after testing multiple thresholds for time cutoffs (30, 60, 90 days) and determining that 30 days had the best discriminatory capacity for the model. Dichotomized hemoglobin to whether hemoglobin was above or below 11 (reference category below) for simplicity of interpretation, after testing multiple cutoffs (7, 8, 9, 10, 11, 12, 13) and determining that 11 had the best discriminatory capacity for the model.

Appendix C - Model selection for aminoglycoside resistance

Table C-1: Model selection for gentamicin/tobramycin resistance in GNRs, comorbidities and demographics

	Comorbidities - start	Comorbidities - end	Comorbidities + demographics - start	Comorbidities + demographics - end
AUROC	0.604	0.593	0.626	0.618
Variable				
CHF	0.111*			
arrhythmia	0.150***			
valve_disease	-0.083			
pulm_vasc_dz	-0.074			
peripheral_vasc_dz	-0.031			
paralysis	0.135*			
neurologic_dz	0.313***	0.387***	0.128*	
chronic_pulm_dz	0.255***	0.303***	0.124	
renal_dz	0.067			
liver_dz	-0.150***			
metastatic_cancer	-0.144*			
tumor_without_mets	-0.232***	-0.28***	-0.271***	
coagulopathy	0.133**			
obesity	0.129*			
weight_loss	0.363***	0.396***	0.457***	0.466***
electrolyte_disorders	0.114**			
blood_loss_anemia	0.114			
deficiency_anemia	-0.078			
renal_failure	0.096			
cystic_fibrosis	1.137***	0.993***	1.178***	1.250***
Asian			0.026	0.004
Black			0.175*	0.198*
Latino			0.274***	0.283***
Other			0.438***	0.453***
in_facility			0.877***	0.912***
_cons	-2.047***	-1.911***	-2.197***	-2.205***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant comorbidities
- Dropped all comorbidities that did not remain significant on multivariable analysis
- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)
- Added in demographic variables (age, gender, race, location prior to admission, etc.)
- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Note: reference category for race is “White”

Table C-2: Model selection for gentamicin/tobramycin resistance in GNRs, combining comorbidities, demographics, and labs together

	Labs - start	Labs - end	Labs + Above
AUROC	0.573	0.569	0.628
Variable			
hemoglobin	-0.064***	-0.061***	-0.062***
platelets	0.000*		
potassium	0.067*		
bicarb	0.022***	0.024***	
GFR	0.002*		
BUN	0.008***	0.007***	
weight_loss			0.429***
cystic_fibrosis			1.295***
Asian			-0.033
Black			0.179*
Latinx			0.274***
Other			0.429***
in_facility			0.921***
_cons	-2.247***	-1.833***	-1.575***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with significant labs

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in end model from above (comorbidities and demographics)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added indwelling devices, none of which improved the model or remained significant on multivariable analysis

Note: reference category for race is “White”

Table C-3: Model selection for gentamicin/tobramycin resistance in GNRs, recent medications plus above variables

	Recent therapy - start	Recent therapy - end	Final model
AUROC	0.597	0.589	0.642
Variable			
last_abx	0.000		
last_aminoglycoside	0.000		
last_ertamero	-0.004***	-0.005***	-0.005***
last_fluoroquin	-0.004***	-0.004***	-0.004***
last_anti_GPC	-0.003***	-0.003***	
last_polymyxin	-0.008***		
last_antacid	0.000		
last_probiotic	-0.003**		
last_chemo	0.000		
last_blood	0.001		
weight_loss			0.420***
in_facility			0.842***
hemoglobin			-0.043***
_cons	0.049	-0.890***	-0.853***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant recent medications

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table C-4: Model selection for gentamicin/tobramycin resistance in GNRs, simplified final model

Final model - simplified	Final model - simplified
AUROC	0.634
Variable	
carb30	0.493***
flo30	0.382***
weight_loss	0.414***
in_facility	0.844***
hem11	-0.232***
_cons	-2.12***

p-values: * <0.05, ** <0.01, *** <0.001

- Dichotomized “last_carbapenem” and “last_fluoroquin” to whether or not antibiotics were received in the prior 30 days for simplicity of interpretation, after testing multiple thresholds for time cutoffs (30, 60, 90 days) and determining that 30 days had the best discriminatory capacity for the model. Dichotomized hemoglobin to whether hemoglobin was above or below 11 (reference category below) for simplicity of interpretation, after testing multiple cutoffs (7, 8, 9, 10, 11, 12, 13) and determining that 11 had the best discriminatory capacity for the model.

Table C-5: Model selection for amikacin resistance in GNRs, comorbidities and demographics

	Comorbidities - start	Comorbidities - end	Comorbidities + demographics - start	Comorbidities + demographics - end
AUROC	0.635	0.631	0.712	0.707
Variable				
CHF	0.067			
arrhythmia	0.210***	0.268***	0.299**	
valve_disease	-0.029			
pulm_vasc_dz	0.005			
peripheral_vasc_dz	0.041			
neurologic_dz	0.288***	0.323***	-0.157	
chronic_pulm_dz	0.251***	0.288***	0.282**	
renal_dz	-0.034			
liver_dz	-0.112			
coagulopathy	0.114			
weight_loss	0.465***	0.504***	0.474***	0.538***
electrolyte_disorders	0.177*			
renal_failure	0.103			
cystic_fibrosis	2.067***	1.982***	1.699***	1.880***
age			-0.011***	-0.009***
male			0.677***	0.664***
in_facility			0.736***	0.742***
ever_icu			0.618***	0.623***
_cons	-3.465***	-3.379***	-3.48***	-3.478***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant comorbidities

- Dropped all comorbidities that did not remain significant on multivariable analysis

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in demographic variables (age, gender, race, location prior to admission, etc.)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table C-6: Model selection for amikacin resistance in GNRs, comorbidities, demographics, and devices

	Comorbidities/demographics + devices - start	Comorbidities/demographics + devices - end
AUROC	0.724	0.710
Variable		
weight_loss	0.449***	0.486***
cystic_fibrosis	1.931***	2.150***
age	-0.008**	
male	0.585***	0.570***
in_facility	0.582***	0.477***
ever_icu	-0.018	
trach	0.097	
ever_vented	0.908***	0.937***
_cons	-3.518***	-4.007***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of comorbidities/demographics from above, added significant indwelling devices

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC).

Table C-7: Model selection for amikacin resistance in GNRs, combining comorbidities, demographics, devices, and labs together

	Labs - start	Labs - end	Labs + Above
AUROC	0.629	0.619	0.723
Variable			
WBC	0.006*		
hemoglobin	-0.148***	-0.146***	-0.053*
platelets	0.000		
sodium	0.017		
potassium	0.077		
chloride	-0.005		
bicarb	0.043***	0.054***	
GFR	0.005***		
BUN	0.008***	0.006***	
glucose	0.000		
weight_loss			0.489***
cystic_fibrosis			2.189***
male			0.563***
in_facility			0.512***
ever_vented			0.887***
_cons	-5.230***	-2.959***	-3.488***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with significant labs

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in end model from above (comorbidities, demographics, and indwelling devices)

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table C-8: Model selection for amikacin resistance in GNRs, recent medications plus above variables

	Recent therapy - start	Recent therapy - end	Final model
AUROC	0.694	0.676	0.733
Variable			
last_abx	0.000		
last_aminoglycoside	-0.003*		
last_ertamero	-0.007***	-0.008***	-0.007***
last_fluoroquin	-0.004***	-0.005***	
last_anti_GPC	-0.008***	-0.009***	-0.006***
last_betalactam	0.001		
last_polymyxin	-0.006***		
last_antacid	-0.004***		
last_probiotic	-0.001		
last_chemo	-0.001		
last_blood	0.001		
cystic_fibrosis			1.992***
male			0.430***
in_facility			0.387***
ever_vented			0.670***
_cons	-0.776**	-1.643***	-2.904***

p-values: * <0.05, ** <0.01, *** <0.001

- Started with list of individually significant recent medications

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

- Added in variables from the above model

- Dropped redundant/collinear variables until parsimony was achieved (no further variables could be dropped without significantly affecting the AUROC)

Table C-10: Model selection for amikacin resistance in GNRs, simplified final model

Final model - simplified	Final model - simplified
AUROC	0.735
Variable	
carb30	0.606***
GPC30	0.529***
cystic_fibrosis	2.037***
male	0.470***
in_facility	0.431***
ever_vented	0.697***
_cons	-4.179***

p-values: * <0.05, ** <0.01, *** <0.001

- Dichotomized “last_carbapenem” and “last_anti_GPC” to whether or not antibiotics were received in the prior 30 days for simplicity of interpretation, after testing multiple thresholds for time cutoffs (30, 60, 90 days) and determining that 30 days had the best discriminatory capacity for the model

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