2016

CLINICAL OUTCOMES ASSOCIATED WITH TIME TO ANTIMICROBIAL THERAPY CHANGE FROM VANCOMYCIN TO DAPTOMYCIN IN STAPHYLOCOCCAL BACTEREMIA

Sarah J. Tennant
University of Kentucky, sarah.tennant@uky.edu
Digital Object Identifier: http://dx.doi.org/10.13023/ETD.2016.298

STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Sarah J. Tennant, Student

Dr. David Feola, Major Professor

Dr. David Feola, Director of Graduate Studies

CLINICAL OUTCOMES ASSOCIATED WITH TIME TO ANTIMICROBIAL THERAPY CHANGE FROM VANCOMYCIN TO DAPTOMYCIN IN STAPHYLOCOCCAL BACTEREMIA

==========

THESIS

==========

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the College of Pharmacy at the University of Kentucky

BY

Sarah J. Tennant, PharmD, BCPS

Lexington, Kentucky

Director: Dr. David Feola, Associate Professor of Pharmacy Practice and Science

Lexington, Kentucky

2016

ABSTRACT OF THESIS

CLINICAL OUTCOMES ASSOCIATED WITH TIME TO ANTIMICROBIAL THERAPY CHANGE FROM VANCOMYCIN TO DAPTOMYCIN IN STAPHYLOCOCCAL BACTEREMIA

Background: *Staphylococcus aureus* is an aerobic, Gram positive commensal organism that is capable of causing a wide spectrum of disease. This study contributes to previously published literature regarding daptomycin versus vancomycin use in *S. aureus* bacteremia (SAB).

Methods: Adult patients admitted between 2010 and 2014, billed for ICD-9 code V09.0, 038.11, 038.12, 041.11, or 041.12, and received vancomycin and daptomycin were included in this retrospective analysis. Patients were stratified by time to change in antibiotics from vancomycin to daptomycin to the early switch (1-3 days), intermediate switch (4-7 days), or late switch (8 days or later) group. The primary outcome was treatment failure defined as 30-day recurrence, 60-day all-cause mortality, and 90-day all-cause readmission.

Results: 193 patients were enrolled in the final cohort. The overall treatment failure rate was 18% with no differences between early switch, intermediate switch, and late switch (P=0.72) groups. Independent predictors of treatment success were length of stay (OR=1.035) and time to positive culture (OR=0.961).

Conclusions: Results of this study did not demonstrate a difference in treatment failure based on time to switch from vancomycin to daptomycin. Future research should focus on optimizing use of vancomycin and daptomycin and medical management of SAB.

KEYWORDS: *Staphylococcus aureus*, vancomycin, daptomycin, outcomes research

Sarah J. Tennant

June 22, 2016

CLINICAL OUTCOMES ASSOCIATED WITH TIME TO ANTIMICROBIAL THERAPY CHANGE FROM VANCOMYCIN TO DAPTOMYCIN IN STAPHYLOCOCCAL BACTEREMIA

By

Sarah J. Tennant, PharmD, BCPS

David J. Feola, PharmD, PhD, BCPS
Director of Thesis/Director of Graduate Studies

June 22, 2016

ACKNOWLEDGEMENTS

"Find a group of people who challenge and inspire you, spend a lot of time with them, and it will change your life. No one is here today because they did it on their own."

– Amy Poehler

The culmination of this project marks the completion of two years of residency training and graduate studies. I have many inspiring and supportive friends and colleagues to thank who have mentored, encouraged, and pushed me along the way. First, thank you to my committee members Dr. David Feola, Dr. Craig Martin, Dr. Val Adams, and Dr. Scott Kincaid. Thank you for making this opportunity a possibility and for keeping me on the path.

Thank you to Dr. David Burgess for pushing me to think critically about this project and for going beyond your comfort zone with this subject matter. You have always been my advocate, even when I have been my own obstacle. Thank you to Mrs. Donna Burgess, for your perspective and a listening ear. The mentorship and friendship from you both over the last three years have made University of Kentucky so special to me.

Thank you to everyone at the Institute for Pharmaceutical Outcomes and Policy for taking this non-traditional graduate student in. Thank you for coffee and ice cream runs, perspective, and data analysis emergencies. Thank you Dr. Jeffery Talbert, Dr. Joshua Brown, Dr. Pratik Doshi, Dr. Cliff Rutter, Nathan Pauly, and Andrew McLaughlin.

Thank you to my co-residents these past two years. You have built me up and brought me back down to earth. We have struggled and strived together to this point, and made some wonderful memories along the way.

Last but not least, thank you to my friends and family and Daniel, for giving me the freedom to forge this non-traditional path. Thank you for listening empathetically and sacrificing your time just as much as I have. I can't wait to bring you all along on the next adventure.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS III

LIST OF TABLES VII

LIST OF FIGURES VIII

CHAPTER ONE: BACKGROUND 1

CHAPTER TWO: RATIONALE, OBJECTIVES, AND SIGNIFICANCE 19

CHAPTER THREE: METHODS 23

Study Design 23

Data Source 24

Definitions 25

Outcomes 26

Statistical Analysis 27

CHAPTER FOUR: RESULTS 29

CHAPTER FIVE: DISCUSSION 36

CHAPTER SIX: CONCLUSION 46

APPENDIX A 47

APPENDIX B 51

APPENDIX C 55

APPENDIX D 59

REFERENCES 60

VITA 78

LIST OF TABLES

TABLE 3.1: CLASSIFICATION SCHEME FOR ACUTE RENAL FAILURE PER RIFLE CRITERIA... 27

TABLE 4.1: BASELINE CHARACTERISTICS OF FINAL COHORT, REPORTED AS N(%) OR MEDIAN (INTERQUARTILE RANGE)..... 30

TABLE 4.2: TREATMENT OUTCOMES, REPORTED AS N(%) 34

TABLE 4.3: ODDS RATIOS DETERMINED BY LOGISTIC REGRESSION RESULTS USING TREATMENT SUCCESS AS THE OUTCOME OF INTEREST. 35

TABLE 4.4: SAFETY OUTCOMES, REPORTED AS N(%) 35

TABLE 5.1: COMPARING TREATMENT OUTCOMES BETWEEN TENNANT, MOORE, AND MURRAY, REPORTED AS N(%) 43

LIST OF FIGURES

FIGURE 1.1: PHARMACOKINETIC AND PHARMACODYNAMIC ILLUSTRATION OF VANCOMYCIN. 8

CHAPTER ONE: BACKGROUND

Staphylococcus aureus is an aerobic, Gram positive bacterium naturally found as a commensal organism on the skin of humans. It especially resides in the nares and can be a facultative anaerobic organism.[1] Once it breaches the barrier of the skin, *S. aureus* can become an opportunistic pathogen capable of causing a wide spectrum of disease in humans including skin and soft tissue infections (SSTIs), osteoarticular infections, pleuropulmonary disease, food poisoning and gastrointestinal upset, meningitis, and bloodstream infection (BSI) and infective endocarditis (IE).[2,3] Surface adhesins on the bacteria mediate adherence to and colonization of end target tissues.[1,2]. Mobile genetic elements are responsible for development of antibiotic resistance mechanisms that have allowed *S. aureus* infections to persist during the antibiotic era. Key mobile genetic elements that will be discussed include *bla* genes which are responsible for beta-lactamase production, and the staphylococcal cassette chromosome (SCC) which is responsible for methicillin resistance.[2,4]

In 1940, penicillin became widely available and revolutionized management of infectious diseases. This prototypical beta-lactam has bactericidal activity by binding to penicillin-binding protein in the cell wall of Gram-positive organisms and inhibiting peptidoglycan cross-linking, thus disrupting cell wall synthesis.[5] By 1942, *S. aureus* demonstrated resistance to penicillin through production of a beta-lactamase enzyme that is capable of hydrolyzing the beta-lactam ring central to penicillin and inactivating the compound.[2,6] Now, more than 85% of *S. aureus* isolates produce this beta-lactamase.[7] There are three

key *bla* genes that confer beta-lactamase production: *blaZ, blaR,* and *blaI*.[2,4] They are encoded on transposons or plasmids and are inducible. Plasmids are auto-replicating DNA molecules that exist separate from the chromosome. *blaR* and *blaI* are regulator genes that also be found on the SCC*mec* that will be discussed in more detail.[2]

In 1959, beta-lactam antibiotics that remained stable against this beta-lactamase were developed with methicillin being the prototypical agent in this antistaphylococcal class. In 1961, methicillin-resistant isolates of *S. aureus* began to emerge.[8] Methicillin resistance is caused by alteration of the beta-lactam binding site at penicillin binding protein (PBP) 2a which has decreased affinity for beta-lactam antibiotics. This altered PBP is encoded by the *mecA* gene SCC*mec*.[2,4] The SCC is a large fragment of DNA that is always inserted into the *S. aureus* chromosome. There are other SCC groups that do not confer methicillin resistance, so these are referred to as non-SCC*mec* groups. All methicillin-resistant *S. aureus* (MRSA) contain one type out of eight SCC*mec* types. These different types are responsible for community-acquired (CA-MRSA) versus hospital-acquired (HA-MRSA), which cause distinct infectious syndromes in different patient populations.[4]

Patients who have come into contact with the healthcare system are at risk for HA-MRSA. Risk factors for HA-MRSA include prolonged hospitalization, stay in the intensive care unit (ICU), prolonged antimicrobial therapy, surgical procedures, and close proximity to a patient in the hospital who is infected or colonized with MRSA. HA-MRSA is often multidrug resistant and causes pneumonias and BSIs.[2,9,10] Roughly 40-

50% of hospital-acquired *S. aureus* isolates are methicillin-resistant.[9] CA-MRSA is acquired from coming into direct contact with the organism through skin-to-skin contact with infected or colonized individuals or contaminated fomites. While some of these individuals may have come into contact with the healthcare system, there have been reports of community-acquired SSTIs in correctional facilities, military personnel, day-care centers, men-who-have-sex-with-men, and athletes.[11,12] CA-MRSA usually causes SSTIs, and can be responsible for necrotizing pneumonia and osteomyelitis.[2,11] CA-MRSA most often contains SCC*mec* type IV which also carries other virulence factors.[2,4] CA-MRSA is resistant to beta-lactam antibiotics, but the other Gram positive-active agents – which are discussed later – retain much activity against CA-MRSA.[11] From a predominantly community-acquired *S. aureus* cohort, 42% of isolates from the bloodstream and 58% of isolates from wounds or abscesses were methicillin-resistant.[13]

Because it is a commensal organism that has the potential to cause opportunistic infections, incidence of *S. aureus* infection is high. A study using administrative data from The Surveillance Network (TSN) Database-USA estimated the rate of *S. aureus*-related hospitalizations at 17.68 per 1,000 hospitalizations in 2009.[14] A study of health plan beneficiaries demonstrated the rate of *S. aureus* SSTIs to be 142.8 per 100,000 years and the rate of *S. aureus* bacteremia (SAB) to be 4.7 per 100,000 patient years.[13] One population based study out of Minnesota estimates an annual incidence of *S. aureus* bacteremia (SAB) of 38.2 per 100,000 person-years over the period between 1998 and 2005.[15] There were no differences in incidence over the seven-year period. However, the incidence of MRSA bacteremia increased significantly in this cohort over the studied

time period from 4.6 per 100,000 person years in 1998 to 10.8 per 100,000 person years in 2005. The authors of this study attributed the increased trend in MRSA to increases in incidence of HA-MRSA, however both CA-MRSA and HA-MRSA are highly incident. The data from the TSN study estimated a rate of 11.74 per 1,000 hospitalizations for MRSA.[14] Overall rate of CA-MRSA was 45% while HA-MRSA was 55%. BSI due to MRSA was responsible for 1.59 per 1,000 hospitalizations; 64% were HA-MRSA and 36% were CA-MRSA. Klevens et al. studied 18 months of data on MRSA reported to the CDC's Emerging Infections Program/Active Bacterial Core surveillance program.[16] Eighty-five percent of MRSA infections were hospital-acquired and 13.7% were community-acquired. BSI (75%), pneumonia (13.3%), and cellulitis (9.7%) were the most common infectious syndromes in this cohort.[16]

S. aureus is also a prominent cause of nosocomial infections. In a study of healthcare-associated infections reported to the Centers of Disease Control and Prevention National Healthcare Safety Network for 2009-2010, *S. aureus* was responsible for 15% of healthcare-associated infections, causing over 12,000 infections.[9] It was the leading causative pathogen for ventilator associated pneumonia and surgical site infections.[9] In the cohort of 8972 cases of invasive MRSA reported by Klevens et al. above, 26.6% were hospital-onset infections.[16] Risk factors for hospital-onset MRSA include previous hospitalization, history of surgery, long-term care residence, and previous MRSA infection or colonization.[16]

Mortality from *S. aureus* bacteremia is considerable. Overall 30-day mortality rate for is estimated at 20% with an attributable mortality rate of 13%, while mortality after one-year is as high as 62%.[17,18] The mortality rate for invasive MRSA infection is estimated at 6.3 per 100,000 patients with higher mortality in persons 65 years and older, African Americans, and males.[16] Multivariate analysis of 1600 episodes of SAB from a retrospective database identified risk factors of mortality to include advanced age, female gender, pneumonia or unknown source of infection, dementia, Charlson score, shock at onset, and arrival to hospital from an institution.[18]

Risk factors for *S. aureus* infection include immunocompromised state, diabetes, substance abuse, and age.[2,14,19] Young persons under the age of 20 years overall had lower hospitalization rates for MRSA than older patients.[14] One risk factor that largely contributes to risk is presence of an intravascular catheter used for dialysis. A study utilizing 2008 data from the CDC's Emerging Infections Program/Active Bacterial Core surveillance system estimated the rate of healthcare-associated, community-onset MRSA bloodstream infections at 404 cases per 10,000 person-years among patients who received dialysis within one year compared to 1.62 cases per 10,000 person-years in all patients included in the database.[20] Intravenous drug users (IVDUs) are at increased risk for *S. aureus* infections due to increased prevalence of nasal colonization, use of contaminated drugs and paraphernalia, and close personal contact within the drug use environment.[21,22] One incidence study conducted in Detroit, MI, showed that *S. aureus* was the causative pathogen in 57% of infections in a cohort of IVDUs with 42% of those *S. aureus* isolates being resistant to methicillin.[23]

Given the high incidence of *S. aureus* infection and high mortality rate, maintaining an effective armamentarium of antistaphylococcal antibiotics is paramount to preventing these rates from increasing. Cell-wall active and rapidly bactericidal agents such as beta-lactams remain the drug of choice against *S. aureus.*[24] Due to the previously described resistance to beta-lactams, other agents with different mechanisms of action have been developed. The virulent and adaptable *S. aureus* has developed resistance to all of them. Presence of the *erm* gene confers resistance to macrolides, lincosamides, and streptogrammin B through alteration of the ribosomal target site on *S. aureus.*[4] Macrolides and sreptogrammins are also susceptible to drug efflux if the *msrA* gene is present.[4] Resistance to the protein synthesis inhibitor linezolid occurs in the presence of the *cfr* gene. This target site-modifying gene confers cross-resistance to chloramphenicol and clindamycin.[2,4] *S. aureus* develops resistance to fluoroquinolones thanks to selective pressure when this Gram-positive bacterium is introduced to subtherapeutic concentrations from doses used to treat a concomitant Gram-negative infection. *S. aureus* develops mutations at the target enzymes in the DNA synthesis process that are inhibited by fluoroquinolones.[25] The folate antagonist combination trimethoprim/sulfamethoxazole (TMP/SMX) becomes ineffective against *S. aureus* when the organism upregulates production of the sulfonamide target *p*-aminobenzoic acid or decreases the binding affinity for trimethoprim to dihydrofolate reductase.[25]

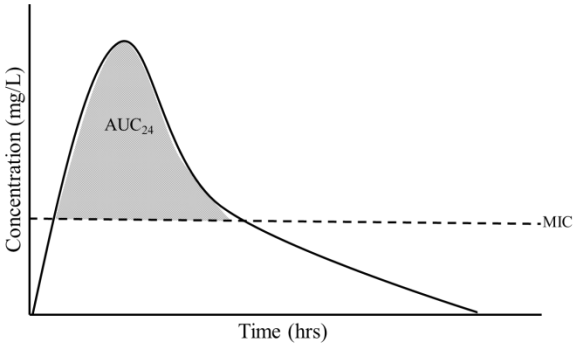
Once the mutated PBP-2a was elucidated as the cause of methicillin resistance in *S. aureus*, this became the target for new beta-lactam development. In 2010, ceftaroline

fosamil was approved for the treatment of SSTIs and community-acquired pneumonia.[26-28] This is the first widely available beta lactam to target the mutation in MRSA, developed almost 50 years after the PBP mutation was discovered. Yet its clinical applications are limited. Its use in clinical practice is often as a second or third line agent for MRSA bacteremia, sometimes in combination with another agent.[29-31] Data on ceftaroline in bacteremia is limited to observational studies and registry databases.[30,32] Ceftaroline binds with high affinity to the mutated PBP-2a in MRSA and thus requires a lower minimum inhibitory concentration (MIC) for clinical success.[33] However, resistant isolates have already emerged during its short period of clinical use.[34]

Vancomycin was first approved in 1958 for treatment of penicillin-resistant *S. aureus*, but after the approval of antistaphylococcal beta-lactams, it became a second line agent.[35] It became a first line agent in the 1980s as MRSA began to emerge and has been widely used since that time.[36] Sorrell et al. described vancomycin for the treatment of MRSA bacteremia in 10 patients and saw no differences in mortality or relapse compared to patients with MSSA who received a beta-lactam.[37] Levine et al. described a cohort of 23 patients with IE caused by CA-MRSA who were treated with vancomycin or a combination of antibiotics including vancomycin and surgery.[38] Sixty-one percent of patients were cured. It exerts its activity by binding to D-alanyl-D-alanine terminal peptide of the peptidoglycan precursors, thus preventing cross-linking in the bacterial cell wall.[39] Compared to beta-lactam agents, vancomycin is slowly bactericidal with a median time to resolution of positive blood cultures of 9 days.[40] Vancomycin requires pharmacokinetic monitoring to ensure both therapeutic efficacy and to monitor patient

safety.[41,42] It is considered a time-dependent killer where optimizing the duration of time that serum concentrations are at a therapeutic level increases antimicrobial effect. When examining a concentration versus time curve, the pharmacodynamic parameter to optimize is a ratio of area-under-the-curve (AUC) to MIC with most studies supporting an optimal AUC/MIC ratio of 400.[43,44] (see **Fig. 1.1**)

Figure 1.1: Pharmacokinetic and pharmacodynamic illustration of vancomycin. Concentration (mg/L) is along y-axis and time in hours is along the x-axis. AUC_{24}=area under the curve over 24 hours (mg/L). MIC=minimum inhibitory concentration (mg/L).[45,46]



Unlike other agents that have been developed to combat *S. aureus*, vancomycin has largely retained its activity over this period of time. In the last 15 years, only 14 isolates of vancomycin-resistant strains of *S. aureus* have been identified globally, with the 14th being confirmed in 2015.[47] Vancomycin resistance is mediated by the plasmid-mediated vanA gene, which causes an amino acid substitution from the D-alanyl-D-alanine target site to D-alanyl-D-lactate, preventing vancomycin binding.[48] *S. aureus* acquired this resistance mechanism through horizontal transmission from *Enterococcus,* an organism with which vancomycin resistance is more common.[48,49]

Importantly, a more common clinical scenario is *S. aureus* strains that are intermediately sensitive to vancomycin. This occurs due to changes in the bacterial cell wall leading to increased cell wall thickness and overproduction of D-alanyl-D-alanine target site. This causes vancomycin to become effectively sequestered in the cell wall of the bacteria and ultimately ineffective.[48,50] One phenomenon that is increasing in prevalence is heterogeneous vancomycin intermediate *S. aureus (*hVISA) where vancomycin-resistant subpopulations exist among predominantly susceptible strains, resulting in increased MICs and failure of vancomycin therapy.[50] Prevalence of hVISA was estimated at 1.2% from a 2011 study of MRSA isolates.[51] Risk factors for developing hVISA include previous vancomycin exposure, high inoculum infections, persistent bacteremia, and subtherapeutic vancomycin serum concentrations.[52-54] HVISA may preclude VISA with repeated vancomycin exposure exerting selective pressure favoring the subpopulations with higher MICs.[55,56] Previous vancomycin exposure and subtherapeutic vancomycin concentrations may play a role in decreased susceptibility with other agents, as will be discussed in a review of daptomycin.

HVISA is speculated to play a role in therapy failure of vancomycin against *S. aureus* when the MIC is at the upper end of the susceptibility range, as reported in multiple studies.[57-60] This led to the 2006 decision by the Clinical Laboratory and Standards Institute to change the vancomycin breakpoints for *S. aureus* so that an MIC $\leq$2 mg/L was considered susceptible, 4-8 mg/L is considered intermediate, and MIC $\geq$16 mg/L is considered resistant.[54] Additionally, multiple centers reported an overall increase in the

vancomycin MICs of the *S. aureus* isolates they were encountering clinically.[61-64] This phenomenon is referred to as the MIC creep. A large study using isolates from international surveillance data from multiple sites of infection was not able to corroborate the occurrence of the MIC creep, however individual centers' epidemiological and clinical factors and susceptibility testing procedures must be considered.[65,66]

With the 2006 changes in vancomycin breakpoints, the accuracy of the different susceptibility testing procedures must be considered in determining the impact of this vancomycin MIC creep. The gold-standard method for determining MIC is broth microdilution (BMD).[67] However, this labor intensive and time consuming methodology is prohibitive to most clinical microbiology labs. As a result, various automated BMD testing methods are available. Compared to standard BMD-identified MIC, manual epsilometer testing (E-testing) and the automated methods may underestimate or overestimate the true MIC.[68-70] This is especially problematic when vancomycin MICs are closer to 2 mg/L. Rybak and colleagues showed 80% agreement between E-testing and BMD when the vancomycin MIC equals 2 mg/L while the automated testing methods ranged from 20%-92% agreement.[68] Bland and colleagues showed that 87% of MRSA isolates had higher vancomycin MICs as determined by E-test than determined by the automated method.[69] Hsu and colleagues looked at vancomycin MIC reporting and clinical outcomes in MRSA infections.[70] In their cohort of patients with MRSA infections, 17 of 21 patients who failed vancomycin therapy had MICs as determined by E-testing >1 mg/L. The agreement between other susceptibility testing methods and E-testing when the MIC >1 mg/L ranged from 9%-80%. The study authors saw more

vancomycin failures at a higher MIC, and E-testing was the most accurate way to determine MIC with a positive predictive value of 89%.[70] Some centers have moved toward E-testing bloodstream isolates of MRSA for a more accurate estimation of vancomycin MIC. However, E-testing tends to be conservative and is interpreted subjectively by microbiology laboratory personnel.

In attempts to answer the question regarding clinical implications of vancomycin MICs at the upper limit of susceptibility in *S. aureus* infections, multiple meta-analyses have been conducted. Three of these meta-analyses concluded that there in an increased risk of mortality and treatment failure with high, but susceptible vancomycin MICs against *S. aureus.*[71-73] However, these meta-analyses are limited by heterogeneous definitions of treatment failure among included studies, different antimicrobial susceptibility testing methods, and multiple sites of infection. In the prominent meta-analysis by van Hal and colleagues the authors stated that their findings were driven by BSIs with vancomycin MIC $\geq$2 mg/L by E-test.[72] A more recent meta-analysis conducted by Kalil and colleagues attempted to specifically examine the driver of treatment failure as defined by van Hal.[74] Their meta-analysis included only *S. aureus* BSIs where the susceptibility was tested by broth microdilution or E-test and examined all-cause mortality as a primary outcome. Analysis did not find an increased absolute risk of mortality when the vancomycin MIC was $\geq$1.5 mg/L. The findings by Kalil and colleagues support current Infectious Diseases Society of America (IDSA) recommendations against using vancomycin MIC only to drive therapy decisions and instead use clinical assessment for management of patients with MRSA bacteremia.[75]

One rationale for treatment failure at these MICs includes limited ability to reach pharmacodynamic targets for optimal bactericidal activity using safe medication doses. As previously mentioned, the pharmacodynamic target for vancomycin therapy is an AUC/MIC ratio of 400. Patel and colleagues performed Monte Carlo simulations to determine both the probability of achieving this pharmacodynamic target at various vancomycin MICs and the probability of nephrotoxicity at various vancomycin dosing regimens.[76] They found that in MRSA infections with vancomycin MIC of 2 mg/L, in order to achieve AUC/MIC $\geq$ 400 80% of the time, one must employ a vancomycin dosing regimen of 2000mg every 12 hours. However, this dosing regimen was associated with a 14% chance of nephrotoxicity in non-ICU patients and a 34% chance of nephrotoxicity in ICU patients. The scenario in which higher doses are required to achieve therapeutic efficacy must be balanced with minimizing adverse events of vancomycin therapy.

Though vancomycin has remained efficacious over time, the aforementioned safety and monitoring limitations led clinicians to develop daptomycin, which is not associated with nephrotoxicity and requires less monitoring. Daptomycin carries indications for SSTI and BSI due to *S. aureus.*[77,78] It has a faster bactericidal mechanism of action and, is administered once daily.[79] Initially developed in 1986, clinical trials were halted due to high occurrence of myalgias and creatine kinase (CK) elevations seen when the drug was administered multiple times per day.[79,80] A new investor and carefully designed safety trials resurrected daptomycin and in 2003 it was approved by the FDA for SSTI.[77] It

works by forming a cationic complex with calcium and binding to bacterial membranes, causing rapid depolarization of membrane potential.[81]

Daptomycin is approved for the treatment of SAB and right-sided IE at a dose of 6 mg per kilogram (kg), however higher doses have been studied. In the randomized controlled trial that garnered its approval, daptomycin 6 mg/kg per day was compared to vancomycin for clinical success at the end of 42 days of therapy. There was no difference between treatment groups with an absolute difference in success rates of 3.4% (95% CI -8.9-15.7).[78] In utilizing the concentration-dependent pharmacodynamics of daptomycin, higher doses have shown good rates of success and low rates of adverse effects. Kullar et al. studied daptomycin dosed 8-10 mg/kg in 250 patients with Gram positive infections and observed an 83.6% clinical success rate.[82] Adverse effects in this cohort were rare with 1.2% of patients experiencing adverse effects and only one patient requiring dose reduction due to CK elevations. A study of 94 registrants from the post-marketing Cubicin Outcome Registry Experience database who received daptomycin 8 mg/kg for Gram positive infections demonstrated an 89% cure rate in clinically evaluable registrants.[83] Adverse effects related to daptomycin occurred in 6.4% of patients including CK elevations occurring in 3.2% of patients, however, these were all deemed not clinically relevant. High-dose daptomycin is efficacious without increased rates of adverse events, and high doses are often utilized in clinical practice.

Since the study by Fowler and colleagues that secure its indication for bacteremia, no clinical trials have demonstrated daptomycin's superiority to vancomycin. However,

some single center, retrospective studies indicate that it may be superior in certain clinical situations. One study by Moore and colleagues examined patients with *S. aureus* who were changed to daptomycin therapy and matched them to patients who completed therapy with vancomycin based on age, Acute Physiology and Chronic Health Evaluation II score, and risk level of source.[84] The decision to change therapy was based on a vancomycin MIC of 1.5 or 2 mg/L as determined by E-test and use of daptomycin at the time was restricted to infectious diseases service. Patients who were switched to daptomycin were switched at a median time of 5 days and the majority was switched due to lack of improvement or worsening on vancomycin. There were no statistically significant differences between groups in a composite outcome of 60-day mortality, microbiological failure, and recurrence (P=0.084), however 60-day mortality was significantly lower (20% vs. 9%, P=0.046) in the group that was switched to daptomycin.[84] Because treatment changes were at the discretion of the treating physician, there may have been selection bias where patients with higher MICs or who were expected to do worse were switched to daptomycin. Additionally, there may have been other factors contributing to poor outcomes. For instance, the study authors did not comment on control of the source of infection between treatment groups. This study does contribute to the question of vancomycin's efficacy against MRSA with higher MICs and whether this may be a potential role for daptomycin.

In another study, Murray and colleagues studied outcomes with early switch to daptomycin based on vancomycin MIC.[85] In accordance with an institutional policy, patients who had MRSA with a vancomycin MIC >1 mg/L received daptomycin as soon

as microbiological susceptibility data was available. Patients who received daptomycin were matched by age, Pitt bacteremia score, and source of bacteremia to patients who received vancomycin. Median duration of vancomycin therapy prior to daptomycin was 1.7 days. Crude analysis showed that daptomycin was superior to vancomycin in a composite outcome of 30-day mortality and occurrence of persistent bacteremia (20% vs. 48.2%, $P<0.001$). This difference remained in multivariable logistic regression where vancomycin patients had 4.5 times higher odds of clinical failure compared to daptomycin. However, one limitation to this study is a change in practice standards as microbiology testing methods changed from E-test to MicroScan during the study period. These susceptibility testing methods are known to have different accuracy in estimating vancomycin MIC.[68] This study excluded central venous access-related infections, so most clinical failures were in deep-seated infections such as IE and bone or joint infections.[85] Widespread application of these studies is limited in that they represent the patient population in one urban city with few comparative studies from other centers. The early transition to daptomycin and minimization of vancomycin exposure resulting in better outcomes is interesting, and the present study seeks to determine if that time to switch plays a role in clinical outcomes.

Decreased susceptibility to daptomycin was seen in the study by Murray and colleagues where 2.6% of patients receiving daptomycin experienced elevated MICs into the non-susceptible range while on therapy.[85] In the clinical trial by Fowler and colleagues, 5% of patients developed reduced susceptibility to daptomycin while on treatment.[78] Daptomycin non-susceptibility (DNS) in *S. aureus* has emerged in less than 10 years

since the antibiotic's approval with the first isolate identified in 2003.[86] DNS is mediated by two mechanisms: an increase in the positive charge of the cell membrane and increased cell wall thickness.[87,88] This increased positivity repels the calcium-daptomycin complex and prevents the antibiotic from getting to its site of action. Increased cell wall thickness prevents daptomycin from reaching the cell membrane. Both resistance mechanisms effectively prevent membrane depolarization and leakage of cell contents leading to cellular death. The clinical understanding of factors leading to emergence of DNS is controversial. While some studies have suggested that it is related to vancomycin exposure, this is an area of continued exploration since results of studies have been mixed.[87,89-91] The potential association between vancomycin exposure and DNS is troubling since clinical guidelines and practice patterns advocate for the use of vancomycin first line followed by daptomycin in patients who experience clinical decline or failure on vancomycin therapy.[75,92]

Decreased daptomycin susceptibility has been observed in VISA isolates. Sader and colleagues examined 207 previously collected *S. aureus* isolates and observed that 47% of VISA isolates were also DNS with MICs > 1mg/L, in contrast to 100% of wild-type MRSA and 100% of hVISA retaining daptomycin susceptibility.[93] Though all hVISA isolates in this study retained susceptibility to daptomycin, hVISA can preclude VISA and thus by extension may preclude DNS.[55] Patel and colleagues reviewed 917 *S. aureus* isolates sent to the CDC.[94] Of 70 isolates with vancomycin MIC between 4 and 16 mg/L, almost 83% of them were DNS.[94] An *in vitro* study by Sakoulas and colleagues demonstrated both development of a vancomycin intermediate phenotype and increasing

daptomycin MICs after 4 isolates of MRSA were exposed to vancomycin.[89] It stands to reason that daptomycin would have decreased activity against VISA because increased cell wall thickness is one of the mechanisms behind DNS and contributes to VISA.[88,95]

The impact of previous vancomycin exposure on daptomycin susceptibility in *S. aureus* isolates with retained vancomycin activity is less replicable. Moise and colleagues conducted a study of 81 clinical MRSA isolates that showed a statistically significant relationship between elevated vancomycin MICs and previous vancomycin exposure (P=0.002) but this relationship was not demonstrated with daptomycin MICs (P=0.111).[87] While Bhalodi and colleagues were able to demonstrate reduced daptomycin activity against an MRSA isolate *in vitro* after the isolate was exposed to vancomycin for 48 hours, they did not detect new DNS subpopulations.[90] Using 5 clinical *S. aureus* isolates that had reportedly become DNS, Rose and colleagues exposed isolates *in vitro* to vancomycin for 4 days followed by daptomycin simulated at 6 mg/kg or 10 mg/kg for 4 days.[91] Daptomycin retained activity against all strains with no difference in time to achieve 99.9% killing between vancomycin pre-exposed and un-exposed simulations. However, daptomycin was more potent against strains that were not pre-exposed to vancomycin.

Until concrete evidence can be elucidated regarding the effect of vancomycin exposure on daptomycin susceptibility in *S. aureus*, clinicians should be optimizing management of *S. aureus* infections to preserve daptomycin's clinical utility and prevent emergence of DNS. Key clinical interventions include taking advantage of concentration-dependent

activity to maximize daptomycin exposure by utilizing high doses, performing early surgery on deep-seated infections with high inoculum to achieve source control, and maintaining therapeutic vancomycin exposure.[92]

CHAPTER TWO: RATIONALE, OBJECTIVES, and SIGNIFICANCE

Staphylococcus aureus is an aerobic, Gram positive bacterium naturally found as a commensal organism on the skin of humans that can become an opportunistic pathogen capable of causing a wide spectrum of disease.[2] With its introduction into clinical practice in 1940, penicillin revolutionized the treatment of infectious diseases, including *S. aureus*; however resistance emerged as soon as 1942.[6] In 1959, antibiotics that remained stable against degrading enzymes produced by the organism were developed, yet in 1961, methicillin-resistant isolates of *S. aureus* began to emerge.[8] Though many antibiotics have been developed to combat *S. aureus*, the organism has developed resistance to most of them and thus they are not utilized first line like vancomycin.

Community-acquired (CA-MRSA) and hospital-acquired (HA-MRSA) cause distinct infectious syndromes in different patient populations. Annual incidence of SAB is estimated between 4.7 and 38.2 per 100,000 patient-years.[13,15] *S. aureus* was responsible for over 12,000 nosocomial infections from 2009-2010.[9] Mortality from SAB is considerable with an overall 30-day mortality rate estimated at 20% and mortality after one-year as high as 62%.[17,18] Risk factors for *S. aureus* infection include immunocompromised state, diabetes, substance abuse, age, presence of central venous catheters, and IV drug use.[2,14,19,20,23]

Vancomycin has been widely used since the 1980s demonstrated an increasing incidence of MRSA, and little resistance has developed in the last 30 years. However, *S. aureus* has developed decreased susceptibility to the drug through alterations in cell wall thickness

and overproduction of antimicrobial targets.[48,50] Individual *S. aureus* microbes with decreased susceptibility can exist as subpopulations of an otherwise susceptible isolates, a phenomenon known as hVISA. Heteroresistance is speculated to play a role in therapy failure of vancomycin against *S. aureus* and an epidemiologic shift to more *S. aureus* isolates have MICs at the upper end of the susceptibility range; however the accuracy of different susceptibility testing procedures must be considered in determining the impact of this vancomycin MIC creep.[68-70] One rationale for treatment failure at higher MICs includes limited ability to reach pharmacodynamic targets for optimal bactericidal activity using safe medication doses.[76] The need to balance the use of efficacious dosing while minimizing adverse events has led individual clinicians to choose alternative therapeutic agents for treatment of MRSA BSI.

Daptomycin carries indications for SSTI and BSI due to *S. aureus*, is not associated with nephrotoxicity, and requires less monitoring. While practice guidelines endorse daptomycin as an alternative to vancomycin, no clinical trials have demonstrated superiority of daptomycin to vancomycin. Current clinical guidelines support a change in therapy guided by patient clinical status.[75] Some single-center studies have suggested better outcomes with daptomycin against SAB with higher vancomycin MICs or when switched early in treatment course.[84,85] Daptomycin non-susceptibility has been encountered clinically and some studies suggest it may be related to previous vancomycin exposure. VISA strains have demonstrated DNS, but this has been less replicable with hVISA strains and vancomycin susceptible strains.[87,89-91,93,94]

The primary objective of this study is to compare clinical outcomes in patients receiving treatment for *S. aureus* bacteremia who switch from vancomycin to daptomycin early (after 1-3 days), intermediately (after 4-7 days), or late (after 8 days or more) in treatment. The central hypothesis of this study is that there are differences in clinical outcomes among patients who switched from vancomycin to daptomycin early, intermediately, and late in therapy for *S. aureus* bacteremia. Clinical failure was defined as recurrent positive blood cultures for *S. aureus* within 30 days of first positive blood culture, death within 60 days after first blood culture positive for *S. aureus*, and all-cause readmission within 90 days after first blood culture positive for *S. aureus*.

Secondary outcomes were to describe the patient population that is switched early, intermediately, and late and to determine what patient factors are associated with treatment failure. Data collected to describe these patients include demographic characteristics, comorbidity measures, severity of illness measures, infection characteristics, concomitant antibiotics received, and safety outcomes measures. Multivariable logistic regression models were constructed to determine independent patient factors associated with treatment failure.

This study is significant because it contributes to previously published literature regarding daptomycin versus vancomycin use in *S. aureus* bacteremia. It further explores previously hypothesized relationships between vancomycin MIC and daptomycin use, and time to switching to daptomycin and patient outcomes. Previous meta-analyses have raised questions regarding vancomycin efficacy in SAB when the vancomycin MIC is

greater than 1 mg/L, and have hypothesized that this could be a niche for daptomycin.[17] One retrospective observational study showed that when vancomycin is switched to daptomycin early based on higher vancomycin MIC, the patients switched to daptomycin had lower clinical failure rates.[85] Patients from this study would fall into the early therapy switch of the present study, and early switch patients will be compared directly to patients who are on vancomycin for a longer period before switching. Additionally, the distribution of vancomycin MICs for *S. aureus* isolates will be observed among groups and if there any differences in outcomes. Another retrospective study showed a mortality benefit when switching from vancomycin to daptomycin intermediately in treatment.[84] The present study will help bridge knowledge gaps from these previous studies by being the first to directly compare patients initiated on vancomycin and switched to daptomycin at different time frames. This study helps determine if the extent of previous vancomycin exposure before switching to daptomycin plays a role in clinical outcomes.

CHAPTER THREE: METHODS

Study Design

A retrospective cohort design was utilized for this study. Patients were included if they were at least 18 years of age at the time of admission, admitted between January 1, 2010, and December 31, 2014, received vancomycin and daptomycin during hospitalization, had an International Classification of Diseases, 9th revision (ICD-9) code of interest billed for during admission, and had *S. aureus* identified from blood culture. Only the first admission per patient during that time period was included for analysis.

Since the study investigator examined patients who were initiated on vancomycin and then therapy was changed to daptomycin, patients had to receive both medications. Medication administration data was utilized to determine duration of therapy. In order to adequately ascertain clinical outcomes, patients were excluded if the total duration of vancomycin and daptomycin was less than 3 days.

ICD-9 codes used to determine enrollment were V09.0 "infection with microorganisms resistant to penicillin", 038.11 "*S. aureus* septicemia", 038.12 "Methicillin resistant *S. aureus* septicemia", 041.11 "*S. aureus* infection, site unspecified", or 041.12 "Methicillin resistant *S. aureus* infection, site unspecified".[96]

Data Source

Subjects were identified and data was collected using the University of Kentucky (UK) Enterprise Data Trust (EDT) through the Center for Clinical and Translational Science (CCTS), which is supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1TR000117. The CCTS EDT is maintained by a biomedical informatics team and the Institute for Pharmaceutical Outcomes and Policy at UK to house clinical data from different electronic systems at UK HealthCare (UKHC). As of December 2015, the clinical data set currently encompasses 554,300 lives admitted as inpatients to UKHC from 2006 on.[97] The EDT has search dimensions for information on demographics, financial classification, provider level detail, medical diagnosis (ICD-9 standard), medical procedures (current procedural terminology [CPT] codes), laboratory tests and results, medications administered, visit details, and vital signs. The UK Institutional Review Board (IRB) has granted umbrella approval for the use of de-identified EDT data for research purposes, and the current study was approved by the UK IRB for use of identified EDT data. Clinical data was collected on identified subjects and is listed in Appendix A. CPT codes for source control procedures are listed in Appendix B. Specific data source variables used in the project are detailed in Appendix C.

Definitions

Patients were stratified based on time to change in therapy from vancomycin to daptomycin. They were *a priori* assigned to the early switch group if therapy was changed after 1-3 days on vancomycin therapy, the intermediate switch group if therapy was changed in 4-7 days, or late switch group if therapy was changed at 8 days or longer.

Time to positive cultures reflects the length of time from admission to diagnosis of bloodstream infection by positive cultures.

A patient was determined to have other infectious organisms if an organism other than *S. aureus* grew from subsequent blood cultures or other tissue samples. Contaminants and colonization were excluded from the definition of other infectious organisms. An isolate was determined to be a contaminant if it grew in blood from only one bottle in a set and did not undergo further microbiological work-up. Isolates determined to represent colonization include *Candida* species or *Enterococcus* species isolated from respiratory sources, less than 100,000 colony-forming units (CFU) of organism from urine, and less than 10,000 CFU of organism isolated from respiratory source. The presence of enteric Gram negative organisms, *Enterococcus* species, or *Candida* species from stool culture also was considered colonization as these organisms represent normal flora.

Treatment failure is defined as all-cause mortality at 60 days from first positive blood culture, recurrence of *S. aureus* in bloodstream within 30 days from initial clearance of blood cultures, or all-cause readmission within 90 days.

Outcomes

The primary outcome is treatment success or treatment failure. Secondary outcomes included the assessment of each individual component defining treatment success or failure and safety outcomes (development of renal injury per RIFLE criteria, diagnosis with *Clostridium difficile* infection, and rhabdomyolysis or creatine kinase elevation >1500 units/mL). Rhabdomyolysis was identified using the ICD-9 code 728.88 "rhabdomyolysis".[98] Use of the ICD-9 code 00.845 "intestinal infection due to *C. difficile*" has been shown to be highly sensitive and specific for identifying *C. difficile* infection.[99]

RIFLE is an acronym for risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease. It is a classification system for assessing acute renal failure. It considers change from baseline, acute on chronic renal disease, sensitivity and specificity, and can be applied across multiple centers.[100] Table 3.1 describes the RIFLE classification for acute renal failure. Glomerular filtration rate was calculated using a modified Cockcroft-Gault equation that omitted body weight from the equation.[101] Temporality for defining loss of kidney

function and end-stage kidney disease could not be assessed, therefore only risk, injury, and failure were assessed as acute kidney injury.

Table 3.1: Classification scheme for acute renal failure per RIFLE criteria[100]

Class	Glomerular Filtration Rate (GFR) Criteria	Urine Output Criteria
Risk	Increased SCr x1.5 or GFR decrease >25%	<0.5 mL/kg/hr x6 hours
Injury	Increased SCr x2 or GFR decrease >50%	<0.5 mL/kg/hr x12 hours
Failure	Increase SCr 3x or GFR decrease 75% or SCr >4 mg/dL	<0.3 mL/kg/hr x24 hours or anuria x12 hours
Loss	Persistent acute renal failure >4 weeks	
End-stage kidney disease	Complete loss of kidney function >3 months	

Statistical Analysis

All statistical comparisons were performed using SAS® version 9.3 (Cary, NC) statistical software. A Shapiro-Wilks test was performed to determine normality and all variables were found to be statistically significantly different from normal, thus nonparametric statistical tests were employed for analysis. Baseline descriptive statistics are reported as median and interquartile range for continuous data or proportions for categorical data. Fisher's exact test will be used to compare distribution of categorical data. Wilcoxon rank sum test will be used to compare distribution of continuous data. The analysis of variance (ANOVA) test was used to compare multiple groups. An alpha level of <0.05 was set to

determine statistical significance. To determine independent predictors of success, a multivariable logistic regression model will be constructed to determine odds ratios with clinical success as the outcome of interest. Backward elimination with an alpha significance level of 0.05 was carried out to determine the final model. The Akaike Information Criterion (AIC) and AUC were used to determine the most predictive model.

CHAPTER FOUR: RESULTS

There were 2,784 admissions for adult patients hospitalized between January 1, 2010, and December 31, 2014 billed for at least one of the including ICD-9 codes. Of those ICD-9 codes, 0.7% of encounters were encoded for V09.0 “infection with microorganisms resistant to penicillin, 7.5% were coded for 038.11 “*S. aureus* septicemia”, 10% were coded for 038.12 “methicillin-resistant *S. aureus* septicemia”, 34.4% were coded for 041.11 “*S. aureus* infection, site unspecified”, and 51% were encoded for 041.12 “methicillin-resistant *S. aureus*, site unspecified”. Three hundred sixty seven patients received at least one dose of both vancomycin and daptomycin. Of that 367, 195 had blood cultures positive for *Staphylococcus aureus*. When patients who received less than 3 days of total therapy were excluded, the final data set included 193 patients. Forty-nine patients (25.4%) were in the early switch group, 76 patients (39.4%) were in the intermediate switch group, and 68 patients (35.2%) were in the late switch group. Baseline characteristics for the final cohort and each treatment group are presented in table 4.1.

Table 4.1: Baseline characteristics of final cohort, reported as n(%) or median (interquartile range)

	Total Cohort N=193	**Early N=49**	**Intermediate N=76**	**Late N=68**	***P*-value**
Gender					
Male	119 (62%)	30 (61%)	49 (64%)	40 (59%)	0.77
Female	74 (38%)	19 (39%)	21 (36%)	28 (41%)	
Race					0.31
White	171 (89%)	43 (88%)	71 (93%)	57 (84%)	
African American	17 (9%)	5 (10%)	3 (4%)	9 (13%)	
Other	5 (2%)	1 (2%)	2 (3%)	2 (3%)	
Age, years	48 (35-59)	50 (36-59)	45.5 (35-59.5)	48 (35-58)	0.68
Charlson comorbidity index	4 (3-7)	5 (3-8)	4 (3-7)	4 (3-6)	0.52
Admitted to intensive care unit	26 (13%)	5 (10%)	10 (13%)	11 (16%)	0.67
History of intravenous drug use	34 (18%)	8 (16%)	16 (21%)	10 (15%)	0.60
Cardiac prosthesis	9 (5%)	2 (4%)	6 (8%)	1 (1%)	0.23
Time to positive culture, days	2.9 (2.0-5.1)	2.1 (1.8-3.5)	2.2 (1.8-3.3)	4.0 (2.0 – 10.0)	0.0005
MRSA	142 (74%)	29 (59%)	64 (84%)	49 (72%)	0.008
Vancomycin MIC, mg/L					0.0016
1	160 (83%)	35 (73%)	57 (80%)	65 (96%)	
2	31 (16%)	12 (25%)	14 (20%)	3 (4%)	
Daptomycin MIC, mg/L					0.45
≤1	189 (98%)	49 (100%)	73 (96%)	67 (99%)	
>1	4 (2%)	0	3 (4%)	1 (1%)	
E-test performed	46 (24%)	13 (27%)	23 (30%)	10 (15%)	0.076
Length of stay, days	24 (13-47)	20 (10-26)	20 (11-39.5)	42 (21.5-55.5)	<0.0001
Source control achieved	71 (37%)	18 (37%)	36 (47%)	17 (25%)	0.021
Cardiac	17	1	13	3	
Skin/soft tissue	3	0	2	1	
Bone/joint	53	14	24	15	
Central venous access	5	3	1	1	
Duration of therapy, days	16 (9-27)	7 (4-16)	13 (8-23.5)	23.5 (15.5-42)	<0.0001

Polymicrobial bloodstream infection	17 (9%)	3 (6%)	5 (7%)	9 (13%)	0.32
Other infectious organisms	80 (41%)	13 (27%)	27 (35%)	40 (59%)	<0.0001
Gram negative	52 (27%)	8 (16%)	18 (24%)	28 (38%)	0.0245
Gram positive	36 (19%)	1 (2%)	13 (17%)	22 (32%)	<0.0001
Fungal from non-urinary source	14 (7%)	3 (6%)	2 (3%)	9 (13%)	0.063
Concomitant MRSA therapy					
Ceftaroline	38 (20%)	12 (24%)	19 (25%)	7 (10%)	0.045
Gentamicin	31 (16%)	8 (16%)	13 (17%)	10 (15%)	0.94
Rifampin	23 (12%)	6 (12%)	10 (13%)	7 (10%)	0.85
Trimethoprim/ Sulfamethoxazole	10 (5%)	0	8 (11%)	2 (3%)	0.023
Other antibiotics					
Cefepime	63 (33%)	17 (35%)	23 (30%)	23 (34%)	0.85
Cefazolin	31 (16%)	9 (18%)	13 (17%)	9 (13%)	0.75
Meropenem	24 (12%)	4 (8%)	10 (13%)	10 (15%)	0.60
Nafcillin	32 (17%)	11 (22%)	11 (14%)	10 (15%)	0.47
Piperacillin/ Tazobactam	119 (62%)	23 (47%)	45 (59%)	51 (75%)	0.0069
Tobramycin or Amikacin	29 (15%)	4 (8%)	7 (9%)	18 (26%)	0.0069
Amphotericin formulation	11 (6%)	0	4 (5%)	7 (10%)	0.046
Daptomycin dose, mg/kg	8.0 (6.0-9.6)	8.6 (6.2-9.7)	8.6 (6.0-9.6)	7.7 (6.0-9.4)	0.56
Initial vancomycin trough, mg/L	13.3 (9.3-23.3	21.5 (11.2-29.8)	13 (8.5-20.6)	13.2 (9.5-23.3)	0.076
Baseline GFR*, mL/min	80.67 (45.67-125.43)	68.50 (41.38-111.86)	80.67 (51.24-131.61)	89.72 (47.16-128.26)	0.14
Baseline CK, units/L	60.5 (27-174)	83 (31.5-189.5)	44 (24-134.5)	62 (27.5-176)	0.70

MRSA=methicillin-resistant *Staphylococcus aureus*
CK=creatine kinase
*****creatinine clearance calculated by modified Cockcroft-Gault equation

Sixty-two percent of the cohort was male. The racial distribution was representative of the largely Caucasian state with whites making up 89%. The cohort was middle aged

with a median age of 48 years (IQR, 35-59 years). Thirteen percent of patients were admitted to the intensive care unit. A history of intravenous drug abuse was reported in 18% of patients. Median length of stay was 24 days, but the late treatment switch group had a significantly longer length of stay of 42 days (P<0.0001). Median time to positive blood cultures from admission was 2.9 days with the late group having a significant longer time to positive cultures of 4.0 days (P=0.0005).

Seventy-four percent of patients in the cohort had MRSA bacteremia, with the early switch therapy group having a significantly lower proportion of MRSA cases at only 54% (P=0.008). While most of these cases (83%) had a vancomycin MIC of 1 mg/L, the late group had significantly higher proportion of isolates with a vancomycin MIC of 1 mg/L (96%, P=0.0016). MICs were tested by E-test for 24% of all *S. aureus* isolates. Daptomycin susceptibility was 98% for the entire cohort. Median time to collection of clear blood cultures was one day. The source of infection was controlled in 37% of the cohort with 47% of patients in the intermediate group achieving source control and only 25% in the late group achieving source control (P=0.021).

Median duration of therapy was 16 days, but duration of therapy was significantly shorter in the early group and longer in the late group (7 days vs. 23.5 days, P<0.0001). Forty-one percent of patients had other infectious organisms identified during hospitalization, and there were significant differences between groups with 59% of patients in the late group growing at least one concomitant organism. Patients in the late group had

significantly more Gram negative, Gram positive, and fungal concomitant organisms compared to patients in the early and intermediate groups. Daptomycin dosing was not significantly different between groups with a median weight-based dose of 8.3 mg/kg for the entire cohort. Median first vancomycin level also did not differ between groups with a median level of 13.1 mg/L. Twenty percent of patients also received ceftaroline during hospitalization, but this was significantly lower in the late group with only 10% of patients receiving concomitant ceftaroline (P=0.045). Five percent of patients received concomitant sulfamethoxazole/trimethoprim, but a significant proportion (11%) of those patients were in the intermediate group (P=0.023). While the majority of patients (62%) in the cohort received piperacillin/tazobactam during hospitalization, there were significantly fewer in the early switch group and significantly more in the late switch group (47% vs. 75%, P=0.0069). Patients in the late switch group also received significantly more amikacin or tobramycin (26% vs. 15%, P=0.0069) and amphotericin (10%vs. 6%, P=0.046) during hospitalization than the overall cohort.

Median baseline creatinine clearance was not different between groups with a value of 98.4 mL/min for the cohort. Median baseline CK value was 60.5 units/L and this did not differ between groups.

Treatment outcomes are reported in table 4.2. Treatment failure occurred in 18% of patients with no differences between groups. None of the components of the definition of treatment failure differed between groups.

Table 4.2: Treatment outcomes, reported as n (%)

	Total Cohort N=193	**Early N=49**	**Intermediate N=76**	**Late N=68**	***P*-value**
30-day recurrence of *S. aureus* from blood culture	2 (1%)	1 (2%)	1 (1%)	0	0.72
60-day mortality	15 (8%)	3 (6%)	6 (8%)	6 (9%)	0.94
90-day readmission	19 (10%)	6 (12%)	6 (8%)	7 (10%)	0.71
Treatment failure	34 (18%)	9 (18%)	13 (17%)	12 (18%)	1.0

Multivariate logistic regression analysis was performed. Variables put into the initial model were for treatment group, history of IV drug use, vancomycin MIC, ceftaroline therapy, sulfamethoxazole/trimethoprim therapy, piperacillin/tazobactam therapy, tobramycin or amikacin use, amphotericin therapy, and other infectious organisms (Appendix D). When performing backwards elimination and using AIC and AUC to determine the final model, time to positive cultures, length of stay, and other infectious organisms provided the model with the best fit (table 4.3). When controlling for other covariates, logistic regression showed that time to positive cultures and length of stay were significant independent predictors of treatment success. For every one day from admission until positive cultures, there was a 4% decreased odds of treatment success (OR 0.961, 95% CI 0.927 – 0.997). For every one additional day spent in the hospital, odds of treatment success increased by roughly 4% (OR 1.036, 95% CI 1.009 – 1.063).

Table 4.3: Odds ratios determined by logistic regression results using treatment success as the outcome of interest.

	Adjusted Odds Ratio Estimate	***95% Confidence Interval***		***P*-value**
Time to positive cultures	0.961	0.927	0.997	0.057
Length of stay	1.036	1.009	1.063	0.0079
Other infectious organisms	0.517	0.225	1.184	0.12

Safety outcomes are reported in table 4.4. The incidence of *C. difficile* was low in the cohort with only 2% of patients being diagnosed during admission. Rhabdomyolysis occurred in 6% of patients. Nephrotoxicity per RIFLE criteria occurred in 43% of patients. There were no differences between groups in occurrence of adverse outcomes. Nephrotoxicity was experience by 41% of patients in the early switch group, 35% of patients in the intermediate group, and 53% of patients in the late switch group (*P*=0.1).

Table 4.4: Safety outcomes, reported as n (%)

	Total Cohort N=193	**Early N=49**	**Intermediate N=76**	**Late N=68**	***P*-value**
Rhabdomyolysis	12 (6%)	3 (6%)	4 (5%)	5 (7%)	0.93
Clostridium difficile	3 (2%)	0	1 (1%)	2 (3%)	0.62
Nephrotoxicity	83 (43%)	20 (41%)	27 (35%)	36 (53%)	0.1

CHAPTER FIVE: DISCUSSION

This study of 193 patients with *S. aureus* bacteremia who initiated treatment on vancomycin and were switched to daptomycin found no difference in patient outcomes based on time to therapy switch. There was no difference in treatment failure between patients switched from vancomycin to daptomycin early after treatment initiation, at an intermediate time frame, or late after initiation for SAB. Unlike previous studies, all patients in the present study were switched from vancomycin to daptomycin rather than having a comparator group that remained on vancomycin. This study accepts the finding from Fowler and Moore that daptomycin is non-inferior to vancomycin, but builds upon the work of Moore and Murray by attempting to further elucidate when daptomycin should be utilized over vancomycin.[78,84,85] The treatment failure rate remains roughly 15-20%, which is consistent with estimates of overall mortality rates of 20%, with mortality one component of most study definitions of clinical failure.[17,102]

Factors that were associated with treatment success were time to positive cultures and length of stay. An extended time to positive cultures was associated with decreased likelihood of clinical success. *S. aureus* is one of the most common organisms isolated in nosocomial-acquired infections.[9] With a median time to positive culture of 4 days in the late switch group, most of the BSIs would meet the definition of nosocomial infection, where the definition is positive blood culture obtained from patients hospitalized for 48 hours or longer.[103] A study by Klevens et al did not demonstrate a higher mortality rate with healthcare-onset SAB vs. community onset SAB, but a study by Cosgrove et al showed that nosocomial SAB is associated with significantly longer length of stay.[16,102]

Longer length of stay was associated with increased likelihood of treatment success as for each day a patient was admitted to the hospital, the odds of treatment success increased by 3%. This is likely a reflection of practice patterns at this institution where patients remain in the hospital for a prolonged period of time to complete therapy. A survey of hospital medicine and infectious diseases physicians conducted at the University of Kentucky revealed that barriers to discharging persons who inject drugs to complete IV antibiotic therapy include socioeconomic factors and the potential risk of the patient misusing the peripherally-inserted central catheter.[104] While participants coded for a history of IV drug use represented a smaller proportion and was not associated with treatment success in the current study population, IV drug use is a known risk factor for developing *S. aureus* infection.[22]

Patients in the late switch therapy group had significantly longer lengths of stay than patients in the early or intermediate switch group. Significantly lower rates of source control and longer durations of antibiotic therapy in the late switch group indicate that these patients likely had complicated bacteremia. Source control is the ultimate cure for SAB.[105-107] The longer length of stay is reflective of the longer duration of antibiotic therapy given practice patterns of the institution as previously discussed. While there were no differences in Charlson comorbidity index or ICU admission to indicate higher severity of illness in the late switch group, these patients more commonly received piperacillin/tazobactam, aminoglycosides, and amphotericin during their admission. They also had more concomitant Gram negative and Gram positive infections indicating they could have had more severe manifestations of infection requiring such broad spectrum

coverage. These agents also cause nephrotoxicity when administered concomitantly with vancomycin, potentially leading to later switch in therapy as nephrotoxic adverse effects began to manifest.[60,108-110] This is supported by a trend toward a higher rate of nephrotoxicity in the late switch group. Nephrotoxicity has been shown to lead to increased lengths of stay.[111,112] Charlson comorbidity index, which is a marker of expected one-year morality, may not be the best indicator of severity of illness in this patient population.[113] However, this index was readily available in the administrative data set, unlike some other markers of illness severity such as Pitt bacteremia score which assesses patients on the day of positive blood cultures and incorporates subjective data such as mental status.[114]

Additional trends where shown between groups with regard to initial vancomycin trough and E-test as the susceptibility method performed. Patients in the early switch group had a higher median initial vancomycin trough level. The median level seen in that group is above the currently recommended therapeutic trough range of 10-20 mg/L.[41,115] High vancomycin trough levels are associated with higher probability of developing nephrotoxicity.[60,76,109,116] Patients in this group may have been proactively switched to daptomycin earlier in early recognition of the potential for nephrotoxicity, especially since they had the lowest baseline GFR. Patients in the late switch group had the lowest proportion of *S. aureus* isolates tested in the clinical microbiology laboratory by E-testing method. For the majority of this study period, susceptibility testing from all blood culture isolates was performed using an automated susceptibility testing method called BD Phoenix™. In summer of 2013 through the end of the study period, the clinical

microbiological lab began performing E-testing on all MRSA isolates from blood culture. Microbiological testing methods are not created equally. BD Phoenix™ tends to underestimate the MIC for vancomycin against *S. aureus* while E-testing tends to be a conservative testing method that often overestimates the MIC.[68,70] Previously published meta-analyses demonstrated adverse clinical outcomes when the vancomycin MIC was greater than 1 mg/L by E-test, which may have led to earlier changes in therapy in the early and intermediate switch groups.[71-73] Clinicians treating patients in the late switch group could have been following current IDSA guidelines to let clinical status rather than MIC guide therapy change decisions, and thus switched therapy to daptomycin in a later time frame.[75]

Another trend existed between groups and concomitant fungal organisms isolated from non-urinary sources. Patients in the late therapy switch group had more non-urinary fungal organisms isolated during hospitalization than patients in the early and intermediate switch groups. Thirteen isolates were *Candida* species. One isolate was a *Cryptococcus neoformans* bloodstream infection. Of the *Candida* isolates, *C. albicans* comprised 23% of fungal isolates. The other 77% were non-*albicans* species with *C. glabrata* making up 46% of the non-*albicans* isolates. Invasive candidiasis comprises *Candida* bloodstream infections and other deep-seated tissue infections due to *Candida* and is associated with a 40% mortality rate.[117] One of the risk factors for invasive candidiasis is broad-spectrum antibiotic use.[117] *Candida* infections represent the 7th most common cause of healthcare-associated infections.[9,118] Patients in the late therapy switch group had significantly higher use of broad-spectrum antibiotic therapy and significantly

longer lengths of stay compared to patients in other groups, and thus were pre-disposed to more fungal infections. While *C. albicans* has historically been the dominant *Candida* species, non-*albicans* species have increased in prevalence. Surveillance data from 40 hospitals located in the Atlanta and Baltimore metropolitan over a 5-year period demonstrated a 64% non-*albicans* rate with *C. glabrata* making up the largest proportion of those isolates; these numbers are comparable to the prevalence of *Candida* species in this cohort.[119]

There are several limitations to consider with this study. First, this was a retrospective study using data that was already collected for the purposes of diagnosis and treatment of disease, not for research purposes. Patients were identified through use of ICD-9 codes submitted for administrative purposes and reimbursement. ICD-9 codes used to determine enrollment were V09.0 "infection with microorganisms resistant to penicillin", 038.11 "*S. aureus* septicemia", 038.12 "Methicillin resistant *S. aureus* septicemia", 041.11 "*S. aureus* infection, site unspecified", or 041.12 "Methicillin resistant *S. aureus* infection, site unspecified".[96] Previously conducted studies using these ICD-9 codes to identify incident *S. aureus* infections from administrative data have demonstrated low sensitivity of 24-65% but high specificity of 99%.[120,121] The low sensitivity for identifying incident infections may be due to errors in coding including history of *S. aureus* infection or colonization. To increase the specificity in this study, the query of encounters with those diagnoses codes were cross-referenced with microbiological data specific for *S. aureus* isolated from blood cultures.

The use of microbiological data could have excluded a substantial proportion of patients referred to this institution from outside institutions. While transferred patients were not excluded explicitly, treatments received at an outside facility may have influenced treatment decisions and patient outcomes at this institution. Transferred patients could only be included if they had blood cultures growing *S. aureus* collected at this institution, leaving opportunity for misclassification of duration of bacteremia and recurrence of infection.

This methodology resulted in a smaller sample size which may limit the external validity of these results to other centers. Data herein represents one tertiary care medical center that serves as a referral center for a large geographical area comprising central and eastern Kentucky. This study would not meet power to detect a meaningful clinical difference in treatment failure between early, intermediate, and late therapy switch as evidenced by the equal rates of treatment failure across groups. Compared to other studies comparing vancomycin and daptomycin, the sample size in this study is comparable in size with less than 200 subjects in total.[84,85]

With respect to assessment of the key response variables, there are a few caveats to consider. The primary outcome consisted of all-cause mortality and all-cause readmission. Due to the limitations of using administrative coding and administrative data to assemble a data set, determining infection-related outcomes would be impractical without conducting retrospective chart review. Because the administrative data set consisted of one clinical data warehouse from one institution, only readmissions to the

studied institution could be ascertained. Additionally, information on outpatient completion of antibiotic therapy could not be ascertained without coordinating data with third party claims databases. Missing values are a routine challenge when working with administrative data and values must be imputed in some cases, which are detailed in Appendix C.

This is the first study to directly compare differences in outcomes based on time to changing therapy and adds to a body of literature comparing vancomycin to daptomycin in clinical practice. Moore and colleagues conducted a study of patients switched from vancomycin to daptomycin after a median of 5 days with the rationale for therapy switch from vancomycin being lack of improvement or worsening on treatment.[84] The primary outcome was clinical failure, a composite of 60-day mortality, persistent bacteremia at 7 days from index culture, and 30-day recurrence. The rate of clinical failure was 17%. Murray and colleagues specifically studied patients who were switched to daptomycin early in the course of therapy based on vancomycin MIC at a median time of 1.7 days.[85] Their composite clinical failure outcome was defined as 30-day mortality and persistent bacteremia. Twenty percent of patients switched to daptomycin experienced clinical failure.

Treatment failure rates from the current study were directly compared to treatment failure rates from the studies by Moore and Murray (table 5.1). Examining the composite of 60-day mortality and 30-day recurrence of MRSA BSI the treatment failure rate in the cohort from Moore and colleagues was 12%. Examining the composite of 30-day mortality, 30-

day recurrence of MRSA BSI, and 30-day readmission, the treatment failure rate in the cohort from Murray and colleagues was 22%. Analyzing these rates compared to treatment failure rates of 18%, 17%, and 18% respectively in the early switch, intermediate switch, and late switch groups in the current study, there was no statistically significant differences in treatment failure between groups (p=0.62). There were no statistically significant differences in mortality or recurrence between the studies. Excluding data from the Moore study since readmission was not an outcome of interest, there were no differences in readmission between the current study and the Murray cohort. There was no difference in treatment failure between the Moore cohort – with a median time to switch of 5 days – and the intermediate switch group in the current study (12% vs. 17%, p=0.47). There was no difference in treatment failure between the Murray cohort – switched at 1.7 days – and the early switch group in the current study (22% vs. 18%, p=0.66).

Table 5.1: Comparing treatment outcomes between Tennant, Moore, and Murray, reported as n (%)[84,85]

	Total Cohort N=337	**Early N=49**	**Inter-mediate N=76**	**Late N=68**	**Moore N=59**	**Murray N=85**	***P*-value**
30-day recurrence of *S. aureus* from blood culture	4 (1%)	1 (2%)	1 (1%)	0	2 (3%)	0	0.23
60-day mortality	23 (7%)	3 (6%)	6 (8%)	6 (9%)	5 (1%)	3 (1%)	0.64
90-day readmission	35 (13%)	6 (12%)	6 (8%)	7 (10%)	--	16 (19%)	0.20
Treatment failure	60 (18%)	9 (18%)	13 (17%)	12 (18%)	7 (12%)	19 (22%)	0.62

-- Readmission was not an outcome of interest in the study by Moore and colleagues.[84]

Future study should move away from comparing daptomycin and vancomycin directly and should instead focus on identifying which patient factors are risk factors for clinical failure, which are associated with clinical success, and how to recognize these as quickly as possible to optimize patient outcomes. The key to vancomycin compared to daptomycin lies in optimizing use of each agent. Vancomycin exposure and subtherapeutic vancomycin levels have been associated with DNS and hVISA isolates.[90,92] Identifying patients who have previously been exposed to vancomycin or who are likely to have suboptimal vancomycin levels may be targets for early initiation of daptomycin. Further clarifying the ideal time to therapy switch and the ideal duration of each vancomycin and daptomycin are other questions to answer.

Paramount to patient success is optimizing management of SAB independent of antimicrobial therapy. Ensuring clearance of bacteremia is vital as persistent staphylococcal bacteremia is associated with 10-times higher risk of relapse and 2.6-times higher odds of in-hospital mortality.[75,122] Patients with relapsed SAB are likely to be re-exposed to vancomycin, and multiple exposures should be minimized to reduce the risk of decreased susceptibility vancomycin and daptomycin. A study by Carugati and the International Collaboration on Endocarditis demonstrated that in patients with MRSA IE, patients definitively treated with daptomycin cleared bacteremia faster than patients treated with standard-of-care regimens, including vancomycin (1.0 day vs. 5.0 days, [$p<0.01$]).[123] This supports switching to daptomycin in persistent bacteremia, though ensuring optimal vancomycin levels is also important to ensuring expedient clearance of blood cultures.[41,124,125] In a case-control study comparing patients with persistent SAB to

patients with resolving bacteremia, initial vancomycin trough less than 15 mg/L was associated with 4-times higher odds of having persistent SAB (OR, 4.25 [95% CI, 1.51-11.96]).[125] Utilizing vancomycin and daptomycin in combination regimens with a beta-lactam for persistent bacteremia is a present topic of several studies.[29,88] As previously discussed, source control to remove nidi of infection is the ultimate cure for SAB.[106,107]

CHAPTER SIX: CONCLUSION

This is the first study to directly compared patients switched from vancomycin to daptomycin for treatment of *S. aureus* bacteremia. Patients were stratified into groups based on early therapy switch (within 1-3 days of starting treatment), intermediate therapy switch (within 4-7 days of starting treatment), or late therapy switch (after 7 days of treatment). This study did not detect a difference in treatment failure rates, defined as 30-day recurrence of *S. aureus* from blood culture, 60-day all-cause mortality after first positive blood culture, or 90-day all-cause readmission after first positive blood culture. Length of stay was positively associated with treatment success while time to positive cultures was negatively associated with treatment success.

Future research directions should focus on optimizing use of vancomycin and daptomycin and medical management of SAB. Previous vancomycin exposure and suboptimal vancomycin concentrations are associated with decreased vancomycin and daptomycin susceptibility. Future studies can identify patients at risk for multiple vancomycin exposures. Which patient factors are risk factors for clinical failure, which are associated with clinical success, and how to recognize these as quickly as possible to optimize patient outcomes are questions that still need to be answered.

APPENDIX A

Clinical Data Points Queried from University of Kentucky HealthCare Enterprise Data Trust

Clinical Data Point	ICD 9 Code (if applicable)
Demographics	
Age at admission	
Gender	
Race	
Admission height	
Admission weight	
Body mass index	
Inpatient location history	
Clinical History	
Charlson comorbidity index	
History of intravenous drug abuse	
Drug dependence	304.xx
Other, mixed, or unspecific drug abuse, unspecified	305.90
Presence of cardiac prosthesis	
Heart valve replaced by other means	V43.3
Automatic implantable cardiac defibrillator *in situ*	V45.02
Cardiac pacemaker *in situ*	V45.01
Osteoarticular source of infection	
Osteomyelitis periostitis and other infections involving bone	730.xx

Infection and inflammatory reaction due to internal joint prosthesis	996.66
Infection and inflammatory reaction due to other internal orthopedic device, implant, or graft	996.67
Abscess of spinal cord	324.1
Other sources of infection	
Bloodstream infection due to central venous catheter	999.32
Infection and inflammatory reaction due to cardiac device, implant, or graft	996.61
Infection and inflammatory reaction due to nervous system device, implant, or graft	996.63
Infection and inflammatory reaction due to indwelling urinary catheter device, implant, or graft	996.64
Infection and inflammatory reaction due to other genitourinary device, implant, or graft	996.65
Infection and inflammatory reaction due to peritoneal dialysis device, implant, or graft	996.68
Infection and inflammatory reaction due to other internal prosthetic device, implant, or graft	996.69

Medication Information

Daptomycin dose, administration date and time, order discontinuation date and time	
Vancomycin dose, administration date and time, order discontinuation date and time	
Dose, administration date and time, order discontinuation date and time for other anti-infective agents	
Aminoglycosides	
Antifungals	
Antituberculosis agents	
Antiviral agents	
Carbapenems	

Cephalosporins

Glycylcyclines

Leprostatics

Lincomycin derivatives

Macrolide derivatives

Miscellaneous antibiotics (aztreonam, colistimethate, dalfopristin-quinupristin, linezolid, metronidazole, polymyxin B)

Penicillins

Quinolones

Sulfamethoxazole/trimethoprim

Microbiology Results

Positive blood cultures

Daptomycin susceptibility

Oxacillin susceptibility

Vancomycin susceptibility

Susceptibility testing method

Laboratory Values

Creatine kinase

Serum creatinine

Vancomycin trough level

Clinical Outcomes

Echocardiogram performed

Infectious diseases service consultation

Cardiac source control procedures

Operations on valves and septa of heart	35.xx
Other operations on heart and pericardium	37.xx
Skin/soft tissue source control procedures	See Appendix B
Osteoarticular source control procedures	See Appendix B
Hospital length of stay	
Discharge status	
Time to readmission	
Date of death	
Safety Outcomes	
Rhabdomyolysis	728.88
Intestinal infection due to *Clostridium difficile*	008.45

ICD 9 - International Classification of Diseases, 9th Revision

APPENDIX B

Current Procedural Terminology (CPT) Codes for Source Control Procedures Queried from University of Kentucky HealthCare Enterprise Data Trust

Procedure	CPT Code Range
Incision and drainage procedures on the skin, subcutaneous, and accessory structures	10040-10180
Debridement procedures on the skin	11000-11047
Biopsy procedures on the skin	11100-11101
Removal of skin tags procedures	11200-11201
Excision-benign lesions procedures on the skin	11400-11471
Excision-malignant lesions procedures on the skin	11600-11646
Skin replacement surgery	1500-15278
Pressure ulcers (decubitus ulcers) procedures	15920-15999
Local treatment procedures for burns	1600-16036
General introduction or removal procedures on the musculoskeletal system	20500-20697
Excision procedures on the neck (soft tissues) and thorax	21550-21632
Repair, revision, and/or reconstruction procedures on the neck (soft tissues) and thorax	21685-21750
Fracture and/or dislocation procedures on the neck (soft tissues) and thorax	21805-21825
Excision procedures on the spine (vertebral column)	22100-22116
Osteotomy procedures on the spine (vertebral column)	22206-22226
Fracture and/or dislocation procedures on the spine (vertebral column)	22305-22328
Arthrodesis procedures of the spine (vertebral column)	22532-22819

Spinal instrumentation procedures on the spine (vertebral column)	22840-22865
Incision procedures on the shoulder	23000-23044
Excision procedures on the shoulder	23065-23229
Introduction or removal procedures of the shoulder	23330-23350
Repair, revision, and/or reconstruction procedures on the shoulder	23395-23491
Fracture and/or dislocation procedures on the shoulder	23500-23680
Arthrodesis procedures on the shoulder	23800-23802
Amputation procedures on the shoulder	23900-23921
Other procedures on the shoulder	23929-23929
Incision procedures on the humerus (upper arm) and elbow	23930-24006
Excision procedures on the humerus (upper arm) and elbow	24065-24115
Introduction or removal procedures on the humerus (upper arm) and elbow	24160-24220
Repair, revision, and/or reconstruction procedures on the humerus (upper arm) and elbow	24300-24498
Fracture and/or dislocation procedures on the humerus (upper arm) and elbow	24500-24685
Arthrodesis procedures on the humerus (upper arm) and elbow	24800-24802
Amputation procedures on the humerus (upper arm) and elbow	24900-24940
Incision procedures on the forearm and wrist	25000-25040
Excision procedures on the forearm and wrist	25065-25240
Introduction or removal procedures on the forearm and wrist	25246-25259
Repair, revision, and/or reconstruction procedures on the forearm and wrist	25260-25492

Fracture and/or dislocation procedures on the forearm and wrist	25500-25695
Arthrodesis procedures on the forearm and wrist	25800-25830
Amputation procedures on the forearm and wrist	25900-25931
Incision procedures on the hand and fingers	26010-26080
Excision procedures on the hand and fingers	26100-26262
Introduction and removal procedures on the hand and fingers	26320-26320
Repair, revision, and/or reconstruction procedures on the hand and fingers	26340-26596
Fracture and/or dislocation procedures on the hand and fingers	26600-26785
Amputation procedures on the hand and fingers	26820-26863
Incision procedures on the pelvis and hip joint	26990-27036
Excision Incision procedures on the pelvis and hip joint	27040-27080
Introduction or removal Incision procedures on the pelvis and hip joint	27086-27096
Repair, revision, and/or reconstruction Incision procedures on the pelvis and hip joint	27097-27187
Fracture and/or dislocation Incision procedures on the pelvis and hip joint	27193-27269
Manipulation procedures on the pelvis and hip joint	27275-27275
Arthrodesis procedures on the pelvis and hip joint	27279-27286
Amputation procedures on the pelvis and hip joint	27290-27295
Incision procedures on the femur (thigh region) and knee joint	27301-27310
Excision procedures on the femur (thigh region) and knee joint	27323-27365

Repair, revision, and/or reconstruction procedures on the femur (thigh region) and knee joint	27380-27499
Fracture and/or dislocation procedures on the femur (thigh region) and knee joint	27500-27566
Manipulation procedures on the femur (thigh region) and knee joint	27570-27570
Amputation procedures on the femur (thigh region) and knee joint	27590-27598
Incision procedure on the leg (tibia and fibula) and ankle joint	27600-27612
Excision procedure on the leg (tibia and fibula) and ankle joint	27613-27647
Repair, revision, and/or reconstruction procedure on the leg (tibia and fibula) and ankle joint	27650-27745
Arthrodesis procedure on the leg (tibia and fibula) and ankle joint	27870-27871
Amputation procedure on the leg (tibia and fibula) and ankle joint	27880-27889
Incision procedures on the foot and toes	28001-28035
Excision procedures on the foot and toes	28039-28175
Removal of foreign body procedures on the foot and toes	28190-28193
Repair, revision, and/or reconstruction procedures on the foot and toes	28200-28360
Fracture and/or dislocation procedures on the foot and toes	28400-28675
Arthrodesis procedures on the foot and toes	28705-28760
Amputation procedures on the foot and toes	28800-28825

APPENDIX C

Variable Definitions and Characteristics

Study Variable	Dataset Variable	Definition
Outcomes Variables		
Treatment failure (primary efficacy outcome)	mort60 + readmit90 + recur30	A composite outcome where if any of those conditions were met, then considered a treatment failure and fail=1
60-day mortality	cx_to_death, cul1, DEATH_DT	Determined by the number of days between first positive blood culture collection and date of death. If missing, then DEATH_DT=999. If $\leq$60 then mort60=1
90-day all-cause readmission	DAYS_TO_READMIT	Days between encounters. If missing, then DAYS_TO_READMIT=999. If $\leq$90 then readmit90=1
30-day recurrence of *S. aureus* from blood culture	cul1, cul2	If days between collection of 1st positive culture and 2nd positive culture after initial clearance $\leq$30 then recur30=1
Clostridium difficile infection (safety outcome)	C_DIFF	Diagnosis based on ICD-9 code, see Appendix A
Rhabdomyolysis (safety outcome)	RHABDOMYOLYSIS, HighCK,	Diagnosis based on ICD-9 code, see Appendix A, creatine kinase(CK) value >1500
Nephrotoxicity (safety outcome)	risk_cr + risk_crcl + inj_cr + inj_crcl + fail_cr + fail_crcl	A composite outcome where if RIFLE criteria were met by serum creatinine or creatinine clearance definitions, then nephrotoxicity=1
Study Covariates		
Gender	GENDR_CD	Derived gender available in EDT
Race	RACE_CD_DES	Derived race available in EDT
Age	AGE	Derived age at time of encounter available in EDT
Charlson comorbidity index	COMORBIDITY_SCORE	Derived severity of illness score available in EDT
Admitted to intensive care unit	ADM2ICU	Derived from admission location available in EDT
History of intravenous drug use	IV_DRUG	Diagnosis based on ICD-9 code, see Appendix A

Cardiac prosthesis	CARDIAC_PROSTHESIS	Diagnosis based on ICD-9 code, see Appendix A
Time to positive culture	cul1, ADMT_DT	Days between admission date and first positive blood culture
Time to clear blood cultures	cul1, cul2	Days between first positive blood culture and last positive blood culture
Methicillin-resistant *S. aureus*	OXA_SUSC, MRSA	If OXA_SUSC=0 then MRSA=1
Vancomycin minimum inhibitory concentration (MIC)	VANMIC	Derived from vancomycin MIC or susceptibility available in EDT. If only reported as susceptible, then VANMIC=1
Daptomycin MIC	DAP_S, DAPTMIC	Derived from daptomycin MIC or susceptibility available in EDT. If only reported as susceptible, then DAPTMIC=1. If only reported as non-susceptible, then DAPTMIC=1.5
E-test performed	MIC_Method	Derived from susceptibility testing method available in EDT
Length of stay	LOS	Derived length of stay available in EDT
Source control achieved	bjsrccntrl, cardsrccntrl, linesrccntrl, source_control	Based on CPT codes, see Appendix B
Duration of therapy	D_DOT + V_DOT	Sum of days of therapy of daptomycin and day of therapy of vancomycin
Polymicrobial bloodstream infection	polymicro_BSI, gram_neg_BSI, gram_pos_BSI, fungal_BSI	Indicates if another organism grew in the same blood culture as a *S. aureus* isolate
Other infectious organisms	other_orgs, other_gram_neg, other_gram_pos,	Indicates if another organism grew from subsequent blood cultures or other tissue samples
Fungal organisms	other_fungal, non_urine_fungal, source, species	Indicates if a fungus grew from subsequent blood cultures or other tissue samples. Describes site of fungal growth and fungal species identified. Fungi was determined to be a urinary source if >100,000

		colony forming units of fungal species grew from urine culture with no concomitant positive blood or non-pulmonary tissue sources
Ceftaroline	CEFTRLN	Indicates ceftaroline was administered during the encounter
Gentamicin	GENTMC	Indicates gentamicin was administered during the encounter
Rifampin	RIFMPN	Indicates rifampin was administered during the encounter
Trimethoprim-Sulfamethoxazole	SMXTMP	Indicates trimethoprim/sulfamethoxazole was administered during the encounter
Cefepime	CEFPM	Indicates cefepime was administered during the encounter
Cefazolin	CEFZLN	Indicates cefazolin was administered during the encounter
Meropenem	MERPNM	Indicates meropenem was administered during the encounter
Nafcillin	NAFCLLN	Indicates nafcillin was administered during the encounter
Piperacillin/Tazobactam	PIPTZB	Indicates piperacillin/tazobactam was administered during the encounter
Tobramycin or Amikacin	Other_AG	Indicates tobramycin or amikacin was administered during the encounter
Amphotericin formulation	AMPHBLIP + ABLC	Indicates an amphotericin B formulation was administered during the encounter
Daptomycin dose	dapto_mg, INIT_WT	First daptomycin dose administered divided by initial weight. If INIT_WT missing, then imputed as standard 70kg
Vancomycin trough	firstvanc_lvl2	First vancomycin trough serum concentration collected

Baseline glomerular filtration rate (GFR)	AGE, FIRST_CRVAL	First GFR calculated using a modified Cockcroft-Gault equation
Baseline creatine kinase (CK)	baselineCK	Derived from first CK value available in EDT

EDT=Enterprise Data Trust

APPENDIX D

Full Logistic Regression Model for Treatment Success Adjusting for Significant Covariates

	Odds Ratio Estimate	95% Confidence Interval		*P*-value
Group	1.043	0.581	1.873	0.8882
Time to positive culture, days	0.967	0.929	1.007	0.1081
Vancomycin MIC, mg/L	1.013	0.293	3.498	0.9839
Length of stay, days	1.023	0.994	1.053	0.1276
Ceftaroline	1.316	0.418	4.149	0.6389
Sulfamethoxazole/Trimethoprim	0.402	0.085	1.892	0.2487
Piperacillin/Tazobactam	1.112	0.468	2.642	0.8099
Tobramycin or Amikacin	2.219	0.514	9.572	0.2853
Amphotericin	0.385	0.074	1.999	0.2562
IV Drug Use	2.425	0.493	11.939	0.2761
Other Infectious Organisms	0.342	0.091	1.279	0.1108
Gram Negative Organisms	3.176	0.833	12.103	0.0905
Gram Positive Organisms	0.684	0.182	2.569	0.5742
Fungal Organisms from Non-Urinary Source	1.213	0.205	7.173	0.8311

REFERENCES

1. Coates R, Moran J, Horsburgh MJ. Staphylococci: colonizers and pathogens of human skin. Future Microbiol 2014;9:75-91.
2. Que Y, Moreillon, P. *Staphylococcous aureus* (including Staphylococcal toxic shock syndrome). In: Bennett J, Dolin, R., Blaser, MJ., ed. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8 ed. Philadelphia, PA: Elsevier; 2015:2237-71.
3. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG, Jr. *Staphylococcus aureus infections:* epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603-61.
4. Malachowa N, DeLeo FR. Mobile genetic elements of *Staphylococcus aureus*. Cell Mol Life Sci 2010;67:3057-71.
5. Fisher JF, Meroueh SO, Mobashery S. Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity. Chem Rev 2005;105:395-424.
6. Rammelkamp CH, Maxon T. Resistance of *Staphylococcus aureus* to the action of penicillin. Proc Soc Exp Biol Med 1942;51:386-9.
7. Jessen O, Rosendal K, Bulow P, Faber V, Eriksen KR. Changing staphylococci and staphylococcal infections. A ten-year study of bacteria and cases of bacteremia. N Engl J Med 1969;281:627-35.
8. Jevons MP, Rolinson GN, Knox R. "Celbenin"-resistant staphylococci. Br Med J 1961;1:124-6.

9. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infect Control Hosp Epidemiol 2013;34:1-14.
10. Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 1982;97:309-17.
11. DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant *Staphylococcus aureus.* Lancet 2010;375:1557-68.
12. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus:* a meta-analysis of prevalence and risk factors. Clin Infect Dis 2003;36:131-9.
13. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010. JAMA 2012;308:50-9.
14. Klein EY, Sun L, Smith DL, Laxminarayan R. The changing epidemiology of methicillin-resistant *Staphylococcus aureus* in the United States: a national observational study. Am J Epidemiol 2013;177:666-74.
15. El Atrouni WI, Knoll BM, Lahr BD, Eckel-Passow JE, Sia IG, Baddour LM. Temporal trends in the incidence of *Staphylococcus aureus* bacteremia in Olmsted County, Minnesota, 1998 to 2005: a population-based study. Clin Infect Dis 2009;49:e130-8.

16. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus infections* in the United States. JAMA 2007;298:1763-71.

17. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* Bacteremia. Clin Microbiol Rev 2012;25:362-86.

18. Yahav D, Yassin S, Shaked H, et al. Risk factors for long-term mortality of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis 2016;35:785-790.

19. Laupland KB, Church DL, Mucenski M, Sutherland LR, Davies HD. Population-based study of the epidemiology of and the risk factors for *invasive Staphylococcus aureus* infections. J Infect Dis 2003;187:1452-9.

20. Kallen AJ, Mu Y, Bulens S, et al. Health care-associated invasive MRSA infections, 2005-2008. JAMA 2010;304:641-8.

21. Tuazon CU, Sheagren JN. Increased rate of carriage of *Staphylococcus aureus* among narcotic addicts. J Infect Dis 1974;129:725-7.

22. Bassetti S, Battegay M. *Staphylococcus aureus* infections in injection drug users: risk factors and prevention strategies. Infection 2004;32:163-9.

23. Crane LR, Levine DP, Zervos MJ, Cummings G. Bacteremia in narcotic addicts at the Detroit Medical Center. I. Microbiology, epidemiology, risk factors, and empiric therapy. Rev Infect Dis 1986;8:364-73.

24. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus bacteremia*. BMC Infect Dis 2011;11:279.

25. Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. J Clin Invest 2003;111:1265-73.

26. Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv41-51.

27. Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv53-iv65.

28. File TM, Jr., Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 2010;51:1395-405.

29. Sakoulas G, Moise PA, Casapao AM, et al. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. Clin Ther 2014;36:1317-33.

30. Casapao AM, Davis SL, Barr VO, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother 2014;58:2541-6.

31. Zasowski EJ, Claeys KC, Casapao AM, et al. Ceftaroline Fosamil (CPT) for the Treatment of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bloodstream

Infections (BSI). San Diego, CA: 55th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2015.

32. Vazquez JA, Maggiore CR, Cole P, Smith A, Jandourek A, Friedland HD. Ceftaroline Fosamil for the Treatment of Bacteremia Secondary to Acute Bacterial Skin and Skin Structure Infections or Community-Acquired Bacterial Pneumonia. Infect Dis Clin Pract (Baltim Md) 2015;23:39-43.
33. Kosowska-Shick K, McGhee PL, Appelbaum PC. Affinity of ceftaroline and other beta-lactams for penicillin-binding proteins from *Staphylococcus aureus* and Streptococcus pneumoniae. Antimicrob Agents Chemother 2010;54:1670-7.
34. Long SW, Olsen RJ, Mehta SC, et al. PBP2a mutations causing high-level Ceftaroline resistance in clinical methicillin-resistant *Staphylococcus aureus* isolates. Antimicrob Agents Chemother 2014;58:6668-74.
35. Griffith RS. Introduction to vancomycin. Rev Infect Dis 1981;3 suppl:S200-4.
36. Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. Antimicrob Agents Chemother 1998;42:1303-4.
37. Sorrell TC, Packham DR, Shanker S, Foldes M, Munro R. Vancomycin therapy for methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 1982;97:344-50.
38. Levine DP, Cushing RD, Jui J, Brown WJ. Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Endocarditis in the Detroit Medical Center. Ann Intern Med 1982;97:330-8.
39. Perkins HR, Nieto N. The significance of D-alanyl-D-alanine termini in the biosynthesis of bacterial cell walls and the action of penicillin, vancomycin and ristocetin. Pure Appl Chem 1973;35:371-82.

40. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. Ann Intern Med 1991;115:674-80.

41. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Sys Pharm 2009;66:82-98.

42. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2009;29:1275-9.

43. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 2011;52:975-81.

44. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet 2004;43:925-42.

45. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-10; quiz 1-2.

46. Nicolau DP. Optimizing outcomes with antimicrobial therapy through pharmacodynamic profiling. J Infect Chemother 2003;9:292-6.

47. Walters MS, Eggers P, Albrecht V, et al. Vancomycin-Resistant *Staphylococcus aureus* - Delaware, 2015. MMWR Morb Mortal Wkly Rep 2015;64:1056.

48. Appelbaum PC. MRSA--the tip of the iceberg Clin Microbiol Infect 2006;12 Suppl 2:3-10.

49. Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. FEMS Microbiol Lett 1992;72:195-8.

50. Fridkin SK. Vancomycin-intermediate and -resistant *Staphylococcus aureus*: what the infectious disease specialist needs to know. Clin Infect Dis 2001;32:108-15.

51. Richter SS, Diekema DJ, Heilmann KP, et al. Activities of vancomycin, ceftaroline, and mupirocin against *Staphylococcus aureus* isolates collected in a 2011 national surveillance study in the United States. Antimicrob Agents Chemother 2014;58:740-5.

52. Howden BP, Ward PB, Charles PG, et al. Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. Clin Infect Dis 2004;38:521-8.

53. Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis 2004;38:448-51.

54. Tenover FC, Moellering JRC. The rationale for revising the clinical and laboratory standards institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. Clin Infect Dis 2007;44:1208-15.

55. Hiramatsu K. Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. Lancet Infect Dis 2001;1:147-55.

56. Liu C, Chambers HF. *Staphylococcus aureus* with heterogeneous resistance to vancomycin: epidemiology, clinical significance, and critical assessment of diagnostic methods. Antimicrob Agents Chemother 2003;47:3040-5.

57. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Jr., Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 2004;42:2398-402.

58. Moise-Broder PA, Sakoulas G, Eliopoulos GM, Schentag JJ, Forrest A, Moellering RC, Jr. Accessory gene regulator group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. Clin Infect Dis 2004;38:1700-5.

59. Maclayton DO, Suda KJ, Coval KA, York CB, Garey KW. Case-control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 microg/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. Clinical Ther 2006;28:1208-16.

60. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 2006;166:2138-44.

61. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol 2006;44:3883-6.

62. Robert J, Bismuth R, Jarlier V. Decreased susceptibility to glycopeptides in methicillin-resistant *Staphylococcus aureus*: a 20 year study in a large French teaching hospital, 1983-2002. J Antimicrob Chemother 2006;57:506-10.

63. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001-05. J Antimicrob Chemother 2007;60:788-94.

64. Rybak MJ, Leonard SN, Rossi KL, Cheung CM, Sader HS, Jones RN. Characterization of vancomycin-heteroresistant *Staphylococcus aureus* from the metropolitan area of Detroit, Michigan, over a 22-year period (1986 to 2007). J Clin Microbiol 2008;46:2950-4.

65. Dhand A, Sakoulas G. Reduced vancomycin susceptibility among clinical *Staphylococcus aureus* isolates ('the MIC Creep'): implications for therapy. F1000 Med Rep 2012;4:4.

66. Jones RN. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin Infect Dis 2006;42:S13-S24.

67. CLSI. M100S: Performance Standards for Antimicrobial Susceptibility Testing. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.

68. Rybak MJ, Vidaillac C, Sader HS, et al. Evaluation of vancomycin susceptibility testing for methicillin-resistant *Staphylococcus aureus*: comparison of Etest and three automated testing methods. J Clin Microbiol 2013;51:2077-81.

69. Bland CM, Porr WH, Davis KA, Mansell KB. Vancomycin MIC susceptibility testing of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* isolates: a comparison between Etest(R) and an automated testing method. South Med J 2010;103:1124-8.

70. Hsu DI, Hidayat LK, Quist R, et al. Comparison of method-specific vancomycin minimum inhibitory concentration values and their predictability for treatment outcome of meticillin-resistant *Staphylococcus aureus* (MRSA) infections. Int J Antimicrob Agents 2008;32:378-85.

71. Mavros MN, Tansarli GS, Vardakas KZ, Rafailidis PI, Karageorgopoulos DE, Falagas ME. Impact of vancomycin minimum inhibitory concentration on clinical outcomes of patients with vancomycin-susceptible *Staphylococcus aureus* infections: a meta-analysis and meta-regression. Int J Antimicrob Agents 2012;40:496-509.

72. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis 2012;54:755-71.

73. Jacob JT, DiazGranados CA. High vancomycin minimum inhibitory concentration and clinical outcomes in adults with methicillin-resistant *Staphylococcus aureus* infections: a meta-analysis. Int J Infect Dis 2013;17:e93-e100.

74. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. JAMA 2014;312:1552-64.

75. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:e18-55.

76. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP. Vancomycin: we can't get there from here. Clin Infect Dis 2011;52:969-74.

77. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38:1673-81.

78. Fowler VG, Jr., Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006;355:653-65.

79. Tally FP, DeBruin MF. Development of daptomycin for gram-positive infections. J Antimicrob Chemother 2000;46:523-6.

80. Oleson FB, Jr., Berman CL, Kirkpatrick JB, Regan KS, Lai JJ, Tally FP. Once-daily dosing in dogs optimizes daptomycin safety. Antimicrob Agents Chemother 2000;44:2948-53.

81. Alborn WE, Jr., Allen NE, Preston DA. Daptomycin disrupts membrane potential in growing *Staphylococcus aureus*. Antimicrob Agents Chemother 1991;35:2282-7.

82. Kullar R, Davis SL, Levine DP, et al. High-dose daptomycin for treatment of complicated gram-positive infections: a large, multicenter, retrospective study. Pharmacotherapy 2011;31:527-36.

83. Moise PA, Hershberger E, Amodio-Groton MI, Lamp KC. Safety and clinical outcomes when utilizing high-dose (> or =8 mg/kg) daptomycin therapy. Ann Pharmacother 2009;43:1211-9.

84. Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. Clin Infect Dis 2012;54:51-8.

85. Murray KP, Zhao JJ, Davis SL, et al. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. Clin Infect Dis 2013;56:1562-9.

86. Jevitt LA, Smith AJ, Williams PP, Raney PM, McGowan JE, Jr., Tenover FC. In vitro activities of Daptomycin, Linezolid, and Quinupristin-Dalfopristin against a challenge panel of Staphylococci and Enterococci, including vancomycin-intermediate *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Microb Drug Resis 2003;9:389-93.

87. Moise PA, Smyth DS, El-Fawal N, et al. Microbiological effects of prior vancomycin use in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2008;61:85-90.

88. Werth BJ, Sakoulas G, Rose WE, Pogliano J, Tewhey R, Rybak MJ. Ceftaroline increases membrane binding and enhances the activity of daptomycin against daptomycin-nonsusceptible vancomycin-intermediate *Staphylococcus aureus* in a

pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother 2013;57:66-73.

89. Sakoulas G, Alder J, Thauvin-Eliopoulos C, Moellering RC, Jr., Eliopoulos GM. Induction of daptomycin heterogeneous susceptibility in *Staphylococcus aureus* by exposure to vancomycin. Antimicrob Agents Chemother 2006;50:1581-5.

90. Bhalodi AA, Hagihara M, Nicolau DP, Kuti JL. In vitro pharmacodynamics of human simulated exposures of ceftaroline and daptomycin against MRSA, hVISA, and VISA with and without prior vancomycin exposure. Antimicrob Agents Chemother 2014;58:672-7.

91. Rose WE, Leonard SN, Sakoulas G, et al. daptomycin activity against *Staphylococcus aureus* following vancomycin exposure in an in vitro pharmacodynamic model with simulated endocardial vegetations. Antimicrob Agents Chemother 2008;52:831-6.

92. Moise PA, North D, Steenbergen JN, Sakoulas G. Susceptibility relationship between vancomycin and daptomycin in *Staphylococcus aureus*: facts and assumptions. Lancet Infect Dis 2009;9:617-24.

93. Sader HS, Fritsche TR, Jones RN. Daptomycin bactericidal activity and correlation between disk and broth microdilution method results in testing of *Staphylococcus aureus* strains with decreased susceptibility to vancomycin. Antimicrob Agents Chemother 2006;50:2330-6.

94. Patel JB, Jevitt LA, Hageman J, McDonald LC, Tenover FC. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *Staphylococcus aureus*. Clin Infect Dis 2006;42:1652-3.

95. Cui L, Tominaga E, Neoh HM, Hiramatsu K. Correlation between Reduced Daptomycin Susceptibility and Vancomycin Resistance in Vancomycin-Intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother 2006;50:1079-82.

96. ICD-9 Code Lookup. Centers for Medicare & Medicaid Services. (Accessed April 21, 2016, at https://www.cms.gov/medicare-coverage-database/staticpages/icd-9-code-lookup.aspx.)

97. University of Kentucky HealthCare Clinical Data. University of Kentucky Center for Clinical and Translational Science, 2015. (Accessed February 4, 2016, at http://www.ccts.uky.edu/ccts/uk-healthcare-clinical-data.)

98. Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. Am J Cardiol 2006;97:61c-8c.

99. Schmiedeskamp M, Harpe S, Polk R, Oinonen M, Pakyz A. Use of International Classification of Diseases, Ninth Revision, Clinical Modification codes and medication use data to identify nosocomial Clostridium difficile infection. Infect Control Hosp Epidemiol 2009;30:1070-6.

100. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.

101. Wilhelm SM, Kale-Pradhan PB. Estimating creatinine clearance: a meta-analysis. Pharmacotherapy 2011;31:658-64.

102. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005;26:166-74.103. Friedman ND, Kaye KS, Stout JE, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791-7.

104. Fanucchi L, Leedy N, Li J, Thornton AC. Perceptions and practices of physicians regarding outpatient parenteral antibiotic therapy in persons who inject drugs. J Hosp Med 2016; doi: 10.1002/jhm.2582. [Epub ahead of print].

105. Aksoy O, Sexton DJ, Wang A, et al. Early surgery in patients with infective endocarditis: a propensity score analysis. Clin Infect Dis 2007;44:364-72.

106. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation 2010;121:1005-13.

107. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;351:1645-54.

108. Rutter WC, Talbert JC, Burgess DB. Incidence of Acute Kidney Injury in Patients Treated with Vancomycin and Piperacillin/Tazobactam. ID Week; 2015; San Diego, CA.

109. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain

troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother 2013;57:734-44.

110. Gomes DM, Smotherman C, Birch A, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. Pharmacotherapy 2014;34:662-9.
111. Kullar R, Davis SL, Taylor TN, Kaye KS, Rybak MJ. Effects of targeting higher vancomycin trough levels on clinical outcomes and costs in a matched patient cohort. Pharmacotherapy 2012;32:195-201.
112. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol 2014;9:12-20.
113. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
114. Chow JW, Fine MJ, Shlaes DM, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991;115:585-90.
115. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

116. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009;49:507-14.
117. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med 2015;373:1445-56.
118. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198-208.
119. Cleveland AA, Harrison LH, Farley MM, et al. Declining incidence of candidemia and the shifting epidemiology of *Candida* resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PloS One 2015;10:e0120452.
120. David MZ, Medvedev S, Hohmann SF, Ewigman B, Daum RS. Increasing burden of methicillin-resistant *Staphylococcus aureus* hospitalizations at US academic medical centers, 2003-2008. *Infect Control Hosp Epidemiol* 2012;33:782-9.
121. Schweizer ML, Eber MR, Laxminarayan R, et al. Validity of ICD-9-CM coding for identifying incident methicillin-resistant *Staphylococcus aureus* (MRSA) infections: is MRSA infection coded as a chronic disease? Infect Control Hosp Epidemiol 2011;32:148-54.
122. Hawkins C, Huang J, Jin N, Noskin GA, Zembower TR, Bolon M. Persistent *Staphylococcus aureus* bacteremia: an analysis of risk factors and outcomes. Arch Intern Med 2007;167:1861-7.

123. Carugati M, Bayer AS, Miro JM, et al. High-dose daptomycin therapy for left-sided infective endocarditis: a prospective study from the international collaboration on endocarditis. Antimicrob Agents Chemother 2013;57:6213-22.
124. Lodise TP, Drusano GL, Zasowski E, et al. Vancomycin exposure in patients with methicillin-resistant *Staphylococcus aureus* bloodstream infections: how much is enough? Clin Infect Dis 2014;59:666-75.
125. Chong YP, Park SJ, Kim HS, et al. Persistent *Staphylococcus aureus* bacteremia: a prospective analysis of risk factors, outcomes, and microbiologic and genotypic characteristics of isolates. Medicine 2013;92:98-108.

VITA

Sarah Joyce Tennant, PharmD, BCPS

Education and Training

University of Kentucky (UK) HealthCare Jul 2014 – Jun 2016
Infectious Diseases Pharmacy Residency
Lexington, KY
Program Director: Scott Kincaid, PharmD, BCPS

UK College of Pharmacy Aug 2014 – Jun 2016
Masters of Science, Pharmaceutical Sciences
Pharmaceutical Outcomes and Policy
Lexington, KY

UK HealthCare Jul 2013 – Jun 2014
PGY-1 Pharmacy Residency
Lexington, KY
Program Director: Aaron Cook, PharmD, BCPS

South Carolina College of Pharmacy Aug 2009 – May 2013
Doctor of Pharmacy
Columbia, SC

University of South Carolina Aug 2008 – May 2009
Pre-pharmacy
Columbia, SC

Greenville Technical College Aug 2006 – May 2008
Associate of Arts, Honors
Associate of Science
Greenville, SC

Certifications and Licensures

Board Certified Pharmacotherapy Specialist Dec 2014
Board of Pharmacy Specialties

Kentucky Registered Pharmacist Jul 2013 – present
License no. 016625

Professional Affiliations

Society of Infectious Disease Pharmacists Aug 2014 – 2015
Inter-Organizational Committee 2014-2015

Infectious Disease Society of America Jun 2014 – 2015

Kentucky Society of Health-Systems Pharmacists (KSHP) Apr 2014 – present

American College of Clinical Pharmacy (ACCP) May 2012 – present
Infectious Diseases Practice and Research Network (ID PRN) Executive Committee, Resident Member 2015-present
Education Affairs Committee 2012-2013

American Society of Health-Systems Pharmacists (ASHP) Oct 2009 – 2015

Publications

Tennant SJ, Burgess DR, Rybak JM, Martin CA. Dec 2015
Utilizing Monte Carlo simulations to optimize institutional empiric antipseudomonal therapy. *Antibiotics*. 2015; 4(4): 643-652.

Editor/Chair Dec 2015
Kentucky Konnection 2015

Tennant SJ, McCreary EK Dec 2015
ID PRN Spotlight in Experts in Training newsletter of ACCP

Tennant SJ, Forster DW, Burgess DR, Huaman MA. Sep 2015
Mycobacterium abscessus prosthetic valve endocarditis in a patient with Marfan Syndrome. *JMM Case Rep.* 2015 Oct; DOI 10.1099/jmmcr.0.000084

Manuscript Referee May 2015
Antimicrob Agents Chemother

Tennant SJ, Hester EK, Caulder CR, Lu ZK, Bookstaver PB. Adherence among Rural HIV-infected patients in the Deep South: A Comparison between Single-Tablet and Multi-Tablet Once-Daily Regimens. *J Int Assoc Provid AIDS Care.* 2015 Jan-Feb; 14 (1): 64-71. Jan 2015

Manuscript Referee Aug 2014
American Journal of Pharmaceutical Education

Engle JP, Erstad BL, Anderson DC Jr, Bucklin MH, Chan A, Donaldson AR, Hagemann TM, OConnell MB, Rodgers PT, **Tennant SJ**, Thomas Z. Minimum qualifications for clinical pharmacy practice faculty. *Pharmacotherapy*. 2014 May; 34 (5): e38-44. — May 2014

Abstracts

Vancomycin versus Daptomycin for Treatment of *Staphylococcus aureus* Bacteremia and Endocarditis in a Cohort of Drug Users — Oct 2015
Tennant SJ, Rutter WC, Kincaid SE, Burgess DS.
ACCP Annual Meeting | San Francisco, CA

Integrating Rapid Diagnostic Testing and Antimicrobial Stewardship into a 24-Hour Pharmacy Resident On-Call Program — Oct 2015
Tennant SJ, Burgess, DR, Ribes JA, Martin CA.
ACCP Annual Meeting | San Francisco, CA

Antimicrobial Stewardship and the Use of Verigene® Gram-Positive and Gram-Negative Rapid Identification System — Oct 2015
Burgess DR, **Tennant SJ**, Ribes JA, Burgess DS.
IDWeek | San Diego, CA

Beyond the Antibiogram: Using Monte Carlo analysis to model institution-specific antipseudomonal therapy — Oct 2014
Tennant SJ, Rybak JM, Burgess DR, Burgess DS, Martin CA
IDWeek 2014 | Philadelphia, PA

Grants

Using Pharmacist-Driven Recommendations to Optimize Management of Staphylococcal Bacteremia — Apr 2015 – Jun 2016
New Investigator | % Effort: 10
Funding Agency: ASHP
Status: In-Progress
Total Cost: $5000

Presentations

First Generation Cephalosporins are First in Line: an update from the infective endocarditis guidelines — May 2016
ACPE no. 0617-9999-16-016-L01-P
KSPH Spring Meeting | Lexington, KY

Case-Based Approach to Examining New and Emerging Therapies for Gram Positive and Gram Negative Infections — May 2015
ACPE no. 0617-999-15-010-L01-P
KSHP Spring Meeting | Lexington, KY

Combination Antimicrobial Strategies in Persistent Bacteremia — Mar 2015
ACPE no. PLS15071-16
UK HealthCare | Lexington, KY

Using Monte Carlo Simulations to Model Institution-Wide Antimicrobial Pharmacodynamics Against *Pseudomonas aeruginosa* — Apr 2014
ACPE no. 0121-9999-14-637-L01-P
Great Lakes Residency Conference | West Lafayette, IN

Clinical Features and Treatment of Nontuberculous Mycobacterium — Jan 2014
ACPE no. 0022-0000-14-002-L01-P
UK HealthCare | Lexington, KY

Awards and Honors

ACCP ID PRN Resident Distinguished Research Travel Award — Aug 2015

IDWeek 2014 Trainee Travel Grant — Jun 2014

KSHP Best Poster — May 2014

Rho Chi Research Day — Apr 2014