Fall 2013

The prevention, treatment, and outcomes of Staphylococcus aureus infections

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THE PREVENTION, TREATMENT, AND OUTCOMES OF *STAPHYLOCOCCUS AUREUS* INFECTIONS

by

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A thesis submitted in partial fulfillment of the
requirements for the Doctor of
Philosophy degree in Epidemiology in
the Graduate College of
The University of Iowa

December 2013

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PH.D. THESIS

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ACKNOWLEDGMENTS

I want to thank my thesis committee members Dr. Eli Perencevich, Dr. Loreen Herwaldt, Dr. Marin Schweizer, Dr. Jeffrey Dawson, Dr. Daniel Diekema, Dr. Tara Smith, and Dr. Elizabeth Chrischilles for their time, knowledge, guidance, and support. I especially want to thank Dr. Daniel Diekema, Dr. Eli Perencevich, Dr. Marin Schweizer, and Dr. Loreen Herwaldt for mentoring me during my graduate education.

I want to acknowledge the many people who assisted with these projects. I thank Melissa Ward, Sandra Cobb, and Martha Freeman for helping with the distribution and management of the IHI MRSA bundle surveys. I thank Dr. Kristie Johnson at the UMMC for assisting with the retrieval of the banked MRSA respiratory specimens and the data abstraction. Additionally, I want to thank Wanita Howard for helping retrieve the banked MRSA respiratory specimens at UIHC. I am extremely grateful to Lan Jiang for tackling the VINCI data and creating a manageable dataset for my thesis project. I specifically want to thank Rick Hollis, Linda Boyken, Cassie Dohrn, Shailesh Tendolkar, Sam Messer, Shapour Riahi, and Kris Heilmann for assisting me with the laboratory projects and for the encouragement and support throughout this entire process.

These projects would have not been possible without the financial support provided by a Grant from the Centers for Disease Control and Prevention (5R18CI000583), a Young Investigator Award from Pfizer #WS79560E, and Dr. Marin Schweizer's VA HSR&D career development award.

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LIST OF ABBREVIATIONS

ACME	Arginine Catabolic Mobile Element
agr	Accessory Gene Regulator
APACHE	Acute Physiology and Chronic Health Evaluation
CA-MRSA	Community-Associated Methicillin-Resistant *S. aureus*
CDC	Centers for Disease Control and Prevention
CI	95% Confidence Intervals
CL	Central Line
HA-MRSA	Healthcare-Associated Methicillin-Resistant *S. aureus*
HR	Hazard Ratios
hVISA	Heterogenous Vancomycin-Intermediate *S. aureus*
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IP	Infection Preventionist
IQR	Interquartile Range
IHI	Institute for Healthcare Improvement
MRSA	Methicillin-Resistant *S. aureus*
MSSA	Methicillin-Susceptible *S. aureus*
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PFGE	Pulsed-Field Gel Electrophoresis
PVL	Panton-Valentine leukocidin
SCC*mec*	Staphylococcal Cassette Chromosome *mec*
SHEA	Society for Healthcare Epidemiology of America
TSST-1	Toxic Shock Syndrome Toxin-1
UIHC	University of Iowa Hospitals and Clinics
UMMC	University of Maryland Medical Center
U.S.	United States of America

VA	Veterans Affairs
VINCI	Veterans Affairs Informatics and Computing Infrastructure

CHAPTER 1

INTRODUCTION

Staphylococcus aureus is an opportunistic pathogen that colonizes the nares of approximately 30% of the U.S. population (1, 2). Until recently, *S. aureus* infections typically occurred in elderly patients who had underlying health conditions and frequent exposure to healthcare settings. However, the incidence of *S. aureus* infections is increasing in healthy children and adults who have not been exposed to healthcare (3-7). *S. aureus* causes a wide array of infections ranging in severity from mild skin infections to severe necrotizing pneumonia. It is a highly adaptive bacterium capable of expressing a variety of resistance mechanisms and virulence factors. These characteristics allow the organism to thrive by evading the host's natural defenses and by protecting itself against exposure to antimicrobial agents.

Results of studies examining the relationship between microbiological characteristics and patient outcomes vary. *S. aureus* carries a variety of resistance mechanisms and virulence factors. For example, the staphylococcal cassette chromosome *mec* (SCC*mec)* provides resistance determinants for multiple antimicrobials while virulence factors such as the Panton-Valentine leukocidin (PVL) toxin damage host cells and inhibit components of the immune system (7, 8). An infection caused by a *S. aureus* isolate that produces such virulence factors may be particularly detrimental to a patient who is recovering from a previous infection like influenza or has a suppressed immune system, and then acquires a staphylococcal infection such as pneumonia. In fact, approximately 25% of influenza-related deaths are due to secondary bacterial infections such as pneumonia (9). If physicians knew exactly which microbiological characteristics are associated with poor clinical outcomes, then perhaps treatment could be altered and/or additional care provided to prevent these outcomes from occurring.

Treating *S. aureus* infections can be challenging because it is not always apparent which treatment option will improve patient outcomes. Bacteremia caused by *S. aureus*

can be especially difficult to treat. Vancomycin is usually prescribed for these infections since it is active against both methicillin-resistant and methicillin-susceptible strains. However, vancomycin treatment failure has been reported, and patients given vancomycin for methicillin-susceptible *S. aureus* (MSSA) infections may have an increased risk of death compared with patients treated with β-lactams (10-13). Therefore, vancomycin may not be appropriate for all patients.

In addition to optimizing antimicrobial therapy for *S. aureus* infections, investigators study methods to prevent infections. In hospitals, MRSA is transmitted from patient to patient on healthcare worker's hands, by contaminated items in the environment (fomites), and occasionally through the air (14-19). Infection prevention and control organizations have developed guidelines to help hospitals reduce hospital-acquired MRSA infections. In 2007, the Institute for Healthcare Improvement's (IHI) 5 Million Lives Campaign included a five-component evidence-based bundle to help reduce transmission of MRSA and infections caused by this organism (20). Most hospitals reporting that the bundle is effective are in urban communities. At present, information is limited on the degree to which rural healthcare facilities have implemented the MRSA bundle.

The objective of these studies was to identify ways to improve outcomes of patients with *S. aureus* infections by investigating microbial characteristics of *S. aureus* and treatment options for patients with *S. aureus* infections. Additionally, methods to prevent *S. aureus* infections from occurring were examined. The following specific aims address all of these components:

Specific Aim 1.1: Examine the association between pathogen characteristics and outcomes of infection among patients with MRSA pneumonia.

> Hypothesis 1.1a: Patients who acquire pneumonia caused by a MRSA strain carrying the PVL genes will have a higher mortality rate than patients infected with a MRSA strain not carrying the PVL genes.

Hypothesis 1.1b: Mortality will be higher for patients who acquire pneumonia caused by a MRSA strain with a dysfunctional *agr* than for patients infected by a strain with a functional *agr*.

Specific Aim 1.2: Examine the association between antimicrobial treatment and outcomes among patients with MRSA pneumonia.

Hypothesis 1.2a: Patients infected with a *S. aureus* strain producing PVL will have a higher mortality rate when treated with vancomycin compared with other antimicrobials.

Hypothesis 1.2b: Patients infected with a dysfunctional *agr S. aureus* strain will have a higher mortality rate when treated with vancomycin compared with patients receiving other antimicrobials.

Specific Aim 2.1: Compare the effectiveness of vancomycin to other anti-staphylococcal antimicrobial agents for empiric treatment of MSSA bacteremia.

Hypothesis 2.1: Patients treated empirically with vancomycin for MSSA bacteremia will have a higher mortality rate compared with patients receiving β-lactams empirically.

Specific Aim 2.2: Compare the effectiveness of vancomycin to other anti-staphylococcal antimicrobial agents for definitive treatment of MSSA bacteremia.

Hypothesis 2.2: Patients receiving definitive treatment with vancomycin for MSSA bacteremia will have a higher mortality rate compared with patients receiving β-lactams for definitive treatment.

Specific Aim 3.1: Determine if the components of the IHI MRSA bundle implemented by Iowa hospitals changed from 2007 to 2011.

Specific Aim 3.2: Identify barriers that prevented Iowa hospitals from implementing components of the IHI MRSA bundle.

Specific Aim 3.3: Identify characteristics of hospitals in Iowa that are associated with implementing components of the IHI MRSA bundle.

Three studies were conducted to examine these aims: 1) A retrospective cohort study evaluated patients who were admitted to two large tertiary care medical centers during 2003-2010 and who had pneumonia caused by MRSA. Susceptibility and molecular testing were performed on the MRSA isolates, and multivariate regression analyses were conducted to identify microbial characteristics, patient characteristics, or antimicrobial treatment as potential predictors of mortality or length of stay. 2) A retrospective cohort study was performed that included patients that had MSSA bacteremia admitted to all Veterans Affairs (VA) hospitals between 2003 and 2011. Multivariable models were created to identify associations between mortality and treatment (vancomycin versus β-lactams). 3) Four cross-sectional surveys focusing on the IHI MRSA bundle were analyzed to determine which bundle components hospitals in Iowa implemented and what barriers hindered the implementation of some bundle components.

Results from these studies can be used to improve patient care by providing additional information on appropriate antimicrobial therapy for patients with MSSA bacteremia. Additionally, healthcare providers can use the results from these studies to improve patient care if they know which microbial characteristics may lead to poor outcomes, and if they understand which infection prevention methods rural hospitals implemented to reduce hospital-acquired MRSA infections. Information gained could also impact current treatment guidelines for *S. aureus* infections and provide benchmark data for infection prevention programs in rural hospitals.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

Brief History of *S. aureus* Infections

S. aureus is a Gram-positive cocci that was identified in 1884 by the German surgeon Anton Rosenbach (21, 22). Before the discovery of penicillin, patients infected with *S. aureus* frequently died. Mortality rates were as high as 82% for patients with *S. aureus* bacteremia (23). Once penicillin was introduced for treating invasive *S. aureus* infections, mortality rates decreased drastically to about 25% (24). However, in the early 1940s, the first penicillin-resistant *S. aureus* strains appeared, and by the end of that decade, approximately 25% of the hospital-associated *S. aureus* strains were resistant to penicillin (25-27). In the 1960s, the antistaphylococcal penicillins, such as methicillin or oxacillin, were developed to treat patients infected with penicillin resistant isolates. Unfortunately, only one year after its introduction, resistant strains emerged in the United Kingdom (28). These strains became known as methicillin-resistant *S. aureus* (MRSA).

During the 1960s-1980s, MRSA hospital-acquired infections sporadically occurred throughout the U. S., but by the early 1990s, 29% of the *S. aureus* hospital-acquired infections were caused by methicillin-resistant strains (29, 30). At first, MRSA was a problem primarily in large urban teaching hospitals, but eventually the organism spread to small rural hospitals as well (29, 30). Within hospitals, patients who were admitted to the ICU, who frequently received antimicrobials, or who were in close proximity to a patient with MRSA had an increased risk of developing a MRSA infection (27, 31, 32).

In the late 1990s, MRSA infections started appearing in patients who had no exposure to the hospital setting. Infections were reported in young, healthy people such as children, athletes, and prisoners (33-36). Furthermore, the MRSA strain causing these infections differed from the MRSA strains circulating within the healthcare system (34-

36). This community-acquired MRSA strain eventually entered and was transmitted within the healthcare system causing hospital-acquired infections (37, 38).

Even though MRSA established itself within the community, it is still primarily a concern in the healthcare setting. From 1974 to 2003, the percent of *S. aureus* infections in intensive care units (ICU) that were caused by methicillin-resistant strains increased from 2% to 64% (30, 39). Hospitalized patients have an increased risk of acquiring a MRSA infection because they often are immunosuppressed, have various comorbidities, have prolonged exposure to antimicrobials, and have indwelling devices such as ventilators or catheters. Additionally, patients colonized with MRSA can develop MRSA infections. Approximately, 30% of the U.S. population carries *S. aureus* in their nares and at least 1.5% of the population carries MRSA (1, 2). *S. aureus* colonizes the nares primarily, but it can also colonize other body sites such as the throat, groin, and skin (40). Patients colonized with MRSA are more likely than patients colonized with methicillin-susceptible *S. aureus* (MSSA) to acquire staphylococcal infections. For example, Davis et al. found a 10-fold increased risk of staphylococcal infection in patients who carried MRSA in their nares compared with patients who carried MSSA or patients who did not carry S. *aureus* in their nares (41).

Currently, infection prevention and control departments within hospitals are working to prevent the transmission of *S. aureus* within their facilities. Many hospitals have implemented programs to improve hand hygiene and environmental cleaning. Some hospitals actively screen patients who are colonized with MRSA. Rates of certain hospital-acquired MRSA infections are declining in some healthcare facilities, potentially due to these infection prevention interventions (42). However, *S. aureus* infections remain common. For example, in the Veteran Affairs (VA) Medical Centers, Caffrey et al. identified a 5% increase in hospital admissions per year for *S. aureus* infections from 2002 to 2009. They also found a 21% increase per year for outpatient visits for these infections during the same time period (43). Additionally, outpatient visits for MRSA

infections rose 37% per year and hospital admissions for these infections rose 14% per year (43). *S. aureus* is a resilient organism, and infections caused by *S. aureus* will continue to be a problem as an aging population is exposed frequently to healthcare.

Hospital-Acquired *S. aureus* Infections

S. aureus, especially MRSA, is a constant clinical concern in acute-care hospital settings. In the past, MRSA primarily infected patients admitted to large urban teaching hospitals, but subsequently MRSA began infecting patients in small or rural hospitals. Panlilio et al. modeled the rates of hospital-acquired MRSA infections for various sized hospitals from 1975 to1991 (30). The percent of *S. aureus* isolates that were resistant to methicillin exceeded 5% in hospitals with ≥ 500 beds in 1983 compared with 1987 in hospitals with ≤ 200 beds (30). As MRSA spread within the hospital setting, the percent of *S. aureus* infections that were caused by methicillin-resistant strains increased within hospital units. Researchers using data from the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance System found that in ICUs the percent of hospital-acquired *S. aureus* infections caused by methicillin-resistant isolates increased from 2.4% in 1975 to 29% in 1991, and increased further to 64% in 2003 (30, 39).

Recently, rates of certain types of hospital-associated *S. aureus* infections have declined. Burton et al. reported a decrease in rates of *S. aureus* central-line-associated bloodstream infections. From 1997-2007, the incidence rate of MSSA central-line-associated bloodstream infections decreased significantly from 0.31 to 0.09 infections per 1000 central line days, and the incidence of MRSA infections decreased significantly from 0.43 to 0.21 infections per 1000 central line days ($P < 0.001$) (42). Additionally, Kallen et al. analyzed data from the CDC's Emerging Infections Program/Active Bacterial Core surveillance system and identified a 9.4% per year decrease in invasive health care-associated MRSA infections from 2005-2008 (44). Healthcare-associated MRSA infection rates may have decreased because hospitals have introduced programs

to improve hand hygiene adherence, have implemented antimicrobial stewardship programs, or have designed interventions to reduce central line infections (45). Additionally, the decreased rates may have been related to natural trends such as changes in predominant strains (45, 46). However, *S. aureus* is still the leading cause of ventilator-associated infections and surgical site infections in the U.S according to data from the National Healthcare Safety Network (47).

Currently, MRSA is one of the most prevalent antimicrobial-resistant organisms causing healthcare-associated infections in the U.S. (48, 49). MRSA is frequently spread in hospitals by patients, healthcare workers, environmental surfaces, and occasionally through the air (14-19). Rates of MRSA infection and transmission within a healthcare facility are affected by factors such as antimicrobial use, healthcare workers' adherence to infection prevention protocols, the rate of MRSA within the community, the number and type of surgical procedures performed, and the patients' overall severity of illness.

MRSA is often resistant to numerous antimicrobial agents, thus treatment options for patients with MRSA infections are limited. For example, many MRSA isolates, particularly healthcare-associated strains, are resistant to chloramphenicol, clindamycin, erythromycin, fluoroquinolones, and trimethoprim-sulfamethoxazole (7). MRSA infections are also associated with increased morbidity and mortality compared with MSSA infections. In fact, Cosgrove et al. found that the mortality rate is two-fold higher for MRSA bacteremia compared with MSSA bacteremia (50). Moreover, patients with MRSA infections have higher attributable healthcare costs than patients with MSSA infections and uninfected patients due to extended lengths of hospital stay, antimicrobial treatment, and, in some cases, surgical procedures to eliminate the infections. MRSA infections cost the U.S. healthcare system approximately $2.5 billion annually (51). Since MRSA infections can be problematic to the patient and healthcare system, we must identify ways to successfully prevent these infections from occurring.

Preventing Hospital-Acquired *S. aureus* Infections

Some infection prevention programs have taken extreme measures to control MRSA. For example, hospitals have remodeled or relocated units to provide MRSA colonized patients private rooms (52-54). Additionally, some states have passed laws mandating active surveillance for patients colonized with MRSA even though various infection prevention organizations, such as the Society for Healthcare Epidemiology of America (SHEA) and the Association for Professionals in Infection Control and Epidemiology, have not supported these regulations (55).

The Healthcare Infection Control Practices Advisory Committee, SHEA, and the Institute for Healthcare Improvement (IHI) have developed evidence-based guidelines to help healthcare workers reduce MRSA transmission in acute care hospitals and in other healthcare facilities (20, 56, 57). The IHI 5 Million Lives Campaign included twelve interventions to reduce harm to hospitalized patients with five interventions focusing on preventing hospital-associated infections (58). One intervention incorporated a five component evidence-based bundle to help reduce MRSA transmission and infections within hospitals (59, 60). The IHI MRSA bundle components included hand hygiene, decontamination of the environment and equipment, active surveillance for colonized patients, contact precautions, and the central line and ventilator bundles (59).

Hand Hygiene

In the 1800s, Dr. Ignaz Semmelweis discovered that if physicians who were examining corpses in the autopsy suite washed their hands before attending to women in labor, rates of puerperal sepsis and death declined (61) The World Health Organization recently created the My Five Moments for Hand Hygiene campaign, which focuses on the points during the patient's care when a healthcare worker should perform hand hygiene: 1) before patient contact; 2) prior to an aseptic task like inserting a catheter; 3) following patient contact; 4) after handling body fluids; and 5) after contact with the patient's environment (62). Unfortunately, hand hygiene compliance rates still remain

low with rates less than 50% in many hospitals (63). Various studies have focused on methods such as enhanced education, performance feedback, and convenient placement of hand hygiene supplies to improve compliance (64-66).

Decontamination of the Environment and Equipment

Surfaces in the environment and on equipment transmit MRSA to patients in the hospital (67-69). Patients may become colonized or infected with MRSA by directly touching a contaminated surface or indirectly by the hands of a healthcare worker who touched a contaminated surface and did not perform proper hand hygiene (67-69). Additionally, fomites, such as computers or stethoscopes, which travel to multiple patient rooms may carry MRSA (70). To eliminate pathogenic organisms, surfaces must be thoroughly cleaned and disinfected by personnel or by systems that produce hydrogen peroxide vapor or ultraviolent light (71). Staff can monitor environmental cleaning by marking surfaces with a fluorescent substance, measuring organic ATP on surfaces, or by observing personnel while they clean (72). Current recommendations address the frequency and adequacy of cleaning and disinfecting progress, but data are limited regarding which method is most effective for monitoring environmental cleaning (72, 73).

Active Surveillance

Patients colonized with MRSA may develop an MRSA infection, or they can transmit the organism to other patients (16, 41, 74). Many infection prevention programs obtain surveillance cultures of patients' nares and of other sites on admission to identify those patients colonized with MRSA. Some programs target specific patient populations or patients admitted to high risk units, like the ICU. Additionally, programs may focus on patients with known risk factors for MRSA colonization such as prior hospitalization, residence in a long-term-care facility, previous MRSA infections, or prolonged exposure to antibiotics (75). Additionally, each hospital needs to determine the most appropriate active surveillance method for their facility based on the availability of laboratory

resources and the number of patient rooms within the unit (76). Healthcare workers should keep patients who may be colonized or infected with MRSA in private rooms until they receive the patient's active surveillance test results from the clinical laboratory. However, this may take hours to days depending on the MRSA detection method performed by the clinical laboratory (76).

Contact Precautions

Healthcare workers implement contact precautions to minimize the spread of resistant organisms, like MRSA, from infected or colonized patients to other patients within the hospital. Contact precautions involve placing infected or colonized patients in private rooms or cohorting them in rooms with patients who are infected or colonized with the same organism (77). Contact precautions also require healthcare workers to wear gowns and gloves when caring for patients colonized or infected with MRSA or with other multidrug-resistant organisms. Healthcare workers should change their gloves if they touch areas that could be contaminated with a large quantity of organisms (77). Additionally, healthcare workers should remove their gowns within the patient's room, and then perform hand hygiene before exiting the room (77). To facilitate adherence, healthcare facilities should place gowns and gloves where they are easily accessible and healthcare workers should discard their gowns and gloves before exiting a patient's room (59). Additionally, it is not necessary for healthcare workers to wear gowns and gloves for all patient care. Harris et al. did not identify a significant difference among MRSA and vancomycin-resistant *Enterococcus* acquisition rates when performing a randomized-trial that compared ICUs which required healthcare workers to where gloves and gowns for all patient contact (21.35 acquisitions per 1000 patient-days to 16.91acquisitions per 1000 patient-days) with ICUs which had healthcare workers follow standard contact precautions guidelines (19.02 acquisitions per 1000 patient-days to 16.29 acquisitions per 1000 patient-days; $P = 0.57$) (78).

Device Bundle

Many medical devices increase the risk of infection by transversing natural barriers, and thereby, allowing organisms access to normally sterile sites. During 2009-2010, approximately 50% of healthcare-associated infections reported to the CDC's National Healthcare Safety Network were central-line-associated bloodstream infections or ventilator-associated pneumonias (79). A central line (CL) is a catheter that is inserted into a vein in the neck, chest, groin, or arm and the catheter tip is in close proximity to the heart (80). CLs allow healthcare workers to dispense medications, fluids, or blood rapidly and to provide intravascular drugs over an extended length of time (80). Patients with central-venous catheters have an increased risk of acquiring bacteremia since the catheter allows pathogens easy access to the circulatory system. In fact, patients undergoing hemodialysis through central venous catheters have a particularly high risk of infection (81). Results of studies have shown that central-line-associated infections may be prevented if healthcare workers use aseptic technique when placing catheters and/or they remove catheters that are no longer needed (82).

Some hospitalized patients are ventilated mechanically. Ventilated patients can acquire pneumonia when they aspirate organisms such as MRSA around their endotracheal tubes into their lungs (83). Healthcare workers can reduce the risk of ventilator-associated pneumonia by performing hand hygiene properly when caring for ventilated patients, weaning the patient from the ventilator as soon as possible, and requiring that ventilated patients perform oral care with chlorhexidine mouthwash or gel (83-84).

Implementing the IHI MRSA bundle

Hospitals throughout the world have implemented the components of the MRSA bundle, but the efficacy of this bundle has been assessed primarily at hospitals in large urban areas. Few studies have examined the implementation of the IHI MRSA bundle within rural facilities even though approximately 1,700 rural hospitals participated in the 5 Million Lives Campaign (85). Additionally, MRSA is endemic within rural

communities (86-88). Therefore, implementing prevention methods, such as the IHI MRSA bundle and monitoring their effectiveness is critical in reducing MRSA within hospitals and also possibly in the community.

Community-Acquired MRSA Infections

From the 1960s through the 1990s, MRSA infections rarely caused infection in the community. However, a large community based MRSA outbreak affected 165 patients from March 1980 to September 1981 in Detroit, Michigan (89, 90). This outbreak began among intravenous drug users, but spread to community residents and to hospitalized patients (89, 90). During this period, the percent of *S. aureus* infections caused by isolates resistant to methicillin rose from 3% to 38% in the Henry Ford Hospital (89, 90).

In the 1990s, healthcare workers began seeing MRSA infections in young, healthy people with no exposure to healthcare (34-36, 91). Herold et al. reported that community-acquired MRSA infections increased from 10 per 100,000 admissions during 1988-1990 to 259 per 100,000 admissions during 1993-1995 among children without risk factors for MRSA infection (36). During the early 1990s to mid-2000s, MRSA caused outbreaks in the community. From 1999-2000, outbreaks of community-acquired MRSA infections affected inmates in prisons and athletes such as fencers, football players, and wrestlers (33, 35). Most patients with community-acquired MRSA infections acquired mild skin and soft tissue infections, but a few patients acquired severe infections like necrotizing fasciitis. In 2003-2004, Miller et al. reported that 29% of patients with MRSA necrotizing fasciitis seen at Harbor-UCLA Medical Center had community-acquired infections (91). None of the 843 patients with MRSA necrotizing fasciiitis included in the study died, but all required intensive surgical and medical treatment (91). Occasionally, community-acquired MRSA infections kill patients, especially children, rapidly (34).

Investigators performed molecular typing on the isolates from the community-acquired MRSA infections and discovered that these strains differed from the strains

circulating within the hospital. The community-associated MRSA (CA-MRSA) strains were often related to the type strains USA300 or USA400, whereas, the healthcare-associated MRSA (HA-MRSA) strains were related to the type strains USA100 or USA200 (7, 92). The CA-MRSA strains usually carried SCC*mec* type IV and were PVL-positive (7, 8, 93). In contrast, HA-MRSA strains usually carried SCC*mec* type II and were PVL-negative (7, 8, 92, 93). Also, CA-MRSA strains were resistant to fewer antimicrobials than were HA-MRSA strains. Recently, some CA-MRSA strains have gained additional resistance determinants (7, 94, 95).

By 2003, CA-MRSA strains were recognized in hospitals (37-39). Seybold et al. determined that 28% of healthcare-associated bloodstream infections at Grady Hospital in Atlanta were caused by strains related to USA300, and Saiman et al. investigated a cluster of breast infections among post-partum women in New York City (37, 38). Now, CA-MRSA strains frequently cause both community-acquired and healthcare-acquired infections, and CA-MRSA strains are spreading rapidly throughout the healthcare system (96-100).

Since MRSA now causes community-acquired infections and hospital-acquired infections, one should examine the epidemiology of MRSA over a region, especially when analyzing the implementation and impact of prevention measures. Most investigators that analyzed interventions to reduce MRSA transmission and MRSA hospital-acquired infections focused on urban hospitals; however, a few studies included both rural and urban hospitals (101-105). Kellie et al. created a statewide collaborative of 13 rural and urban healthcare facilities in New Mexico to reduce MRSA bacteremia by focusing on active surveillance testing, hand hygiene, contact precautions, and enhanced environmental cleaning (105). These investigators found that the collaborative reduced hospital-acquired MRSA bacteremias from 0.79 per 10,000 patient days in 2007 to 0.41 per 10,000 patient days in 2009 (105). However, we need additional studies to analyze MRSA prevention methods across regions or states within the U.S. These studies are

especially critical as the U.S. population is aging because elderly persons frequently are exposed to healthcare, and they can acquire severe MRSA infections, like bacteremia, endocarditis, or pneumonia.

S. aureus Pneumonia

S. aureus is a major cause of hospital-acquired pneumonia, and MRSA causes approximately 20%-40% of hospital-acquired pneumonia and of ventilator-associated pneumonia (106, 107). Hospitalized patients have an increased risk of developing *S. aureus* pneumonia because they typically have multiple comorbidities, have suppressed immune systems, are ventilated, or have had previous MRSA infections. Additionally, patients who carry MRSA in their respiratory tracts can aspirate the organism into their lungs and subsequently, they may develop MRSA pneumonia (108, 109). A survey of 402 healthcare facilities found that skin and soft tissue infections were the most common MRSA infections and pneumonia was the second most common MRSA infections (110).

Until the late 1990s, *S. aureus*, specifically MRSA, rarely caused pneumonia outside of the hospital setting. In 1997-1999, the CDC received reports of two children with community-acquired MRSA pneumonia who were not previously exposed to healthcare (34). These children had necrotizing pneumonia, and they died within seven days of hospitalization (34). Throughout the 2000s, cases of community-acquired MRSA pneumonia occurred in young, healthy people. During the 2003-2004 influenza seasons, Hageman et al. identified 17 patients with *S. aureus* community-acquired pneumonia, 15 patients were infected with methicillin-resistant isolates (111). Twelve of the patients had laboratory-confirmed influenza infections (111). The infections progressed rapidly with five deaths occurring within one week of symptom onset (111). In 2006-2007, clinicians identified a cluster of MRSA community-acquired pneumonia that affected 10 patients in Georgia and Louisiana (112). Patients were young (median age: 17.5 years), and most had laboratory-confirmed influenza (60%) (112). Sixty percent of the patients died, and the time to death ranged from 2 to 25 days with a median of 3.5 days (112).

Many patients that die from pneumonia are co-infected with bacteria and influenza or were infected with influenza and subsequently become infected with bacteria. Twenty-five percent of influenza-related deaths are caused by secondary bacterial infections, such as *S. aureus* pneumonia (9). Furthermore, many deaths during the 1918-1919 influenza pandemic were likely caused by secondary bacterial pneumonia (113). Recently, clinicians reported death among patients who had both bacterial pneumonia and the 2009 pandemic H1N1 influenza (114-117).

The fatality rate for *S. aureus* pneumonia can be as high as 75% due to necrosis of lung tissue (118). However, researchers disagree on which bacterial factors damage lung tissue leading to poor outcomes, including death. Additionally, results of studies examining the relationship between pathogenic characteristics and patient outcomes vary.

Panton-Valentine leukocidin (PVL) is a pore-forming exotoxin that destroys polymorphonuclear neutrophils (119-121). Various studies of either patients or animal models have examined the association between PVL and adverse outcomes; however, results have varied substantially. Gillet et al. and Labanderia-Ray et al. first noted that severe necrotizing pneumonia was associated with the presence of PVL (118,122). Both groups described patients with severe pneumonia and assessed the role of PVL within mouse models (118, 122). Moreover, Diep and colleagues observed that lung necrosis, pulmonary edema, alveolar hemorrhage, and mortality were higher in rabbits infected with a PVL-positive *S. aureus* strain compared with a PVL-negative mutant strain (119). However, other investigators have not found significant differences in clinical outcomes or mortality caused by PVL-positive strains compared with those caused by PVL-negative strains (123, 124). Peyrani et al. conducted a multicenter observational study and found that MRSA pneumonia caused by PVL-positive strains was not associated with higher mortality compared with pneumonia caused by PVL-negative strains ($P > 0.99$) (123). Similarly, Sharma-Kuinkel et al. found that clinical outcomes were similar for

patients with hospital-acquired pneumonia caused by PVL-positive *S. aureus* strains compared with those infected with PVL-negative strains (124).

The accessory gene regulator (*agr*) controls the expression of various housekeeping genes and virulence factors. In mouse models, the *agr* locus has been associated with fatal pulmonary infection, necrotizing pneumonia, and bacteremia (125, 126). The loss of *agr* has been associated with increased polystyrene adherence and biofilm production (127, 128). Also, a dysfunctional *agr* has been associated with higher mortality in patients with *S. aureus* bacteremia (129). Pathogenic factors such as the arginine catabolic mobile element (ACME) and USA type have been linked to severe MRSA pneumonia, but these characteristics have not been examined as extensively as PVL and *agr*. Researchers found toxin-shock syndrome toxin-1 present in *S. aureus* isolates from patients co-infected with influenza and *S. aureus* pneumonia (130). Montgomery et al. measured the expression of *agr*, hla, and PVL in rats that had pneumonia, and found increased expression among USA300 strains compared with USA400 strains (131). Additionally, ACME may contribute to the pathogenicity of *S. aureus* strains related to USA300 (132, 133).

S. aureus Bacteremia

S. aureus is also a common cause of bacteremia (44). Bacteremia, also known as a bloodstream infection, occurs when bacteria invade the bloodstream (134, 135). If the site or source of infection is unknown, the patient is said to have a primary bloodstream infection (135-137). If the patient has a preexisting or concurrent *S. aureus* infection, such as a skin and soft tissue infection, surgical wound infection, or pneumonia then the patient's bloodstream infection is said to be secondary to the preexisting or concurrent *S. aureus* infection (135-137). As previously mentioned, indwelling devices such as central lines increase the risk for bacteremia.

Bacteremia is the most common infection caused by *S. aureus* (138). In fact, 75% of 8,792 invasive *S. aureus* infections reported to the Active Bacterial Core surveillance

system were bloodstream infections (138). Data from the CDC's National Healthcare Safety Network indicated that *S. aureus* is the second most common cause of catheter-associated bloodstream infections in the U.S. (79). Risk factors for acquiring a *S. aureus* bacteremia include older age, male gender, receiving hemodialysis, and frequent contact with the healthcare system (139).

Factors, such as gender, age, immune status, comorbidities, the source of infection, and the strain of *S. aureus* affect the risk of death (139). Males are more likely to acquire a *S. aureus* bacteremia while females are twice as likely to die from a *S. aureus* bacteremia (38, 138-145). van Hal et al. hypothesized that females may have a higher risk due to their health behaviors, differences in infecting strains, or hormonal differences (139). Additionally, multiple studies have identified an association between increased age and mortality; however, the odds of mortality differ between studies (139). Patients who are immunocompromised also have an increased risk of death (139, 146, 147). For example, Kaech et al. found a 4-fold higher odds of death for immunocompromised patients compared with immunocompetent patients (147). Specific comorbidities, such as alcoholism, cirrhosis, congestive heart failure, malignancy, and chronic renal failure, have been associated with mortality (139). Some of these underlying diseases impair immune function and others decrease the patient's ability to respond to the physiological and metabolic demands of bloodstream infections, thereby increasing the risk of death in patients with bacteremia.

Additionally, patients with multiple comorbidities have increased risk of acquiring *S. aureus* bacteremia (139). In patients with secondary bloodstream infections, the primary source of infection may be a risk factor for mortality. Mortality rates for patients with a *S. aureus* pulmonary infections range from 39% to 67%, and morality rates for patients with *S. aureus* endocarditis range from 25% to 60% (139).

Poor outcomes, like mortality, can potentially be avoided by removing the source of infection, such as an infected catheter or implant, draining the site of infection (e.g. an

abscess), or surgically removing infected issue. Additionally, implementing treatment and receiving appropriate antimicrobial therapy may reduce the risk of acquiring unfavorable outcomes. Patients with MRSA bacteremia have limited options for appropriate treatment, and outcomes among patients with methicillin-susceptible bloodstream infections who are treated with an antimicrobial targeted for MRSA are worse than those for patients treated with a β-lactam agent (10-13).

Treatment for *S. aureus* Infections

Selecting Antimicrobial Therapy

Healthcare workers can have difficulty selecting antimicrobial therapy for *S. aureus* infections because MRSA, which cause a high proportion of *S. aureus* infections in hospitalized patients, are often resistant to many antimicrobial classes (148). Vancomycin is typically prescribed for patients with invasive MRSA infections or for patients suspected of having an MRSA infection because, currently, only a few MRSA isolates are resistant to vancomycin. To date, approximately 11 MRSA isolates have been confirmed to be vancomycin resistant in the U.S. (149). Nevertheless, researchers have observed a "MIC creep" which could increase the incidence of resistant strains (150). Furthermore, vancomycin may not be an appropriate treatment for all patients with a MRSA infection. Vancomycin has several important limitations: it is not bactericidal, it does not penetrate well into lung tissue, and it can cause serious adverse effects, including nephrotoxicity and red man syndrome.

Vancomycin was first introduced for the treatment of penicillin-resistant *S. aureus* infections in 1958 (150). However, it was rarely used until the 1980s when the incidence of MRSA infections began to increase (151). Today, organizations such as the Infectious Diseases Society of America (IDSA) recommend vancomycin for the treatment of some MRSA infections (152). However, the literature varies regarding which treatment is optimal for patients with invasive MRSA infections. Vancomycin is usually prescribed for patients with invasive infections such as bacteremia or pneumonia.

Linezolid is another antimicrobial agent used to treat complex MRSA infections. Yanagihara et al. examined a mouse model of MRSA pulmonary infection and found that mice treated with linezolid had lower concentrations of viable bacteria in their lungs and a lower mortality rate than mice treated with vancomycin (153). A randomized controlled study that treated 1,184 patients with either linezolid or vancomycin for hospital-acquired pneumonia found a significantly higher rate of clinical success in patients treated with linezolid, but the mortality rates were similar in the two treatment groups (154). Additionally, nephrotoxicity occurred more frequently among patients treated with vancomycin (18.2%) than among those treated with linezolid (8.4%) (154). Moore et al. found a lower rate of clinical failure, mortality, microbiologic failure, and reoccurrence among bacteremic patients treated with daptomycin compared with patients treated with vancomycin (155). Also, ceftaroline, a newer antimicrobial agent, might be a good option for treating MRSA infections since most MRSA strains are currently susceptible to this drug (156).

Even though clinicians typically prescribe vancomycin for MRSA infections, this agent is not effective for all patients possibly due to pathogenic characteristics of the MRSA strain. For example, vancomycin treatment failure has been associated with *agr* dysfunction. One study identified a dysfunctional *agr* in 58% of heterogenous vancomycin-intermediate *S. aureus* (hVISA) isolates compared with only 12.5% for vancomycin-susceptible *S. aureus* isolates ($P = 0.02$) (157). In contrast, linezolid inhibits production of virulence factors, such as staphylococcal enterotoxins A and B, protein A, and α-hemolysin (60). Similarly, Micek et al. described improved clinical outcomes in patients with MRSA pleuropulmonary infections who received antimicrobials that inhibit exotoxin expression (linezolid or clindamycin) (158). Further studies need to examine the interaction of the organism's pathogenic characteristics and the efficacy of treatment for MRSA infections in order to improve patient outcomes.

Empiric and Definitive Treatment

Empiric treatment is defined as the antimicrobials prescribed for patients before the causative organism has been identified whereas definitive treatment is defined as the antimicrobials prescribed for patients after the organism is identified. Patients who received inappropriate therapy or whose appropriate therapy was delayed may have poor outcomes. Lin et al. identified an association between delay in antimicrobial therapy and mortality among patients with bacteremia, with the highest odds of mortality among patients who had neutropenia who were not admitted to the ICU (OR: 17.3; CI: 2.65-113.5) (159). Additionally, Lodise et al. reported a 4-fold increased odds of mortality for patients who had hospital-acquired *S. aureus* bacteremia and whose treatment was delayed compared with patients who received prompt treatment (OR: 3.8; CI: 1.3-11.0) (160). Furthermore, Gomez et al. found an 8-fold increased odds of mortality among patients with MRSA bacteremia who received inappropriate empiric treatment compared with patients who received appropriate treatment (OR: 7.6; CI: 1.87-31.14) (161).

Conversely, other investigators did not find an association between poor outcomes and empiric treatment. Kaasch et al. identified a protective effect for 30-day mortality (OR: 0.52; CI: 0.19-1.45) and severe sepsis or septic shock (OR: 0.51; CI: 0.22-1.19) among patients with delayed appropriate antimicrobial therapy (162). Additionally, Schweizer et al. reported a reduced hazard of mortality for patients with an extended time to appropriate therapy (HR: 0.79; CI: 0.60-1.03), although the relationship was inversed among the healthiest patients (HR: 1.44; CI: 0.66-3.15) (163).

Some researchers speculate that the type of antimicrobial prescribed for empiric therapy may impact patients' outcome. Schweizer et al. found a 79% lower mortality hazard for patients with MSSA bacteremia that received nafcillin or cefazolin compared with vancomycin (10). Additionally, patients with MSSA bacteremia who originally received vancomycin and were switched to a β-lactam had a 69% lower mortality hazard compared with patients treated only with vancomycin (10). Moreover, several studies have found lower mortality rates and lengths of hospitalization for patients infected with

S. aureus who received antimicrobial agents such as linezolid or daptomycin for empiric therapy compared with patients receiving vancomycin (161, 164). Thus, investigators need to conduct further epidemiologic studies so that they can identify ideal empiric and definitive antimicrobial therapy for specific *S. aureus* infections.

CHAPTER 3

PREDICTORS OF POOR OUTCOMES AMONG PATIENTS WHO HAVE METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* PNEUMONIA

Abstract

Background: Methicillin-resistant *S. aureus* (MRSA) pneumonia is associated with poor clinical outcomes. If factors associated with unfavorable outcomes can be identified, interventions that target these factors could be implemented. The aim of this study is to determine which microbial, patient, or treatment factors were associated with poor outcomes among patients with MRSA pneumonia.

Methods: This retrospective cohort study included patients admitted to two large tertiary care medical centers during 2003-2010 who had an ICD-9-CM code for pneumonia and an available MRSA respiratory or blood isolate. Pulsed-field gel electrophoresis (PFGE), accessory gene regulator (*agr*) function testing, staphylococcal cassette chromosome *mec* (SCC*mec*) typing, and detection of Panton-Valentine leukocidin (PVL), arginine catabolic mobile element (ACME), and toxic shock syndrome toxin-1(TSST-1) were performed on the isolates. Patient data was collected from the electronic medical records. Multivariable models were created using Cox proportional hazards regression and ordinal logistic regression to identify predictors of mortality or length of stay.

Results: The 30-day mortality for MRSA pneumonia was 18% (23/131). Patients who died were more likely to be older than 54 years (78% vs. 41%; $P = 0.001$), to be admitted to an intensive care unit (ICU) (87% vs. 46%; $P < 0.001$), and to receive vancomycin (74% vs. 44%; $P = 0.010$) than those who survived. By multivariable analysis, increased age (> 54 years) (hazard ratio (HR): 4.49; 95% confidence interval (CI): 1.64-12.33), ICU admission (HR: 5.25; CI: 1.52-18.21), and hospital-onset pneumonia (HR: 0.32; CI: 0.13-0.75) were associated with mortality. Admission to the ICU (odds ratio (OR): 7.34; CI: 3.58-15.04), increased age (> 54 years) (OR: 2.27; CI: 1.19-4.35), hospital-onset

pneumonia (OR: 3.60; CI: 1.26-10.28), and vancomycin treatment (OR: 10.85; CI: 3.68-32.00) were associated with longer length of stay.

Conclusions: Admission to the ICU, increased age, hospital-onset pneumonia, and vancomycin treatment were associated with poor outcomes in our study. None of the microbial characteristics were associated with poor outcomes.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging etiology for community-acquired pneumonia and a frequent cause of healthcare-acquired and ventilator-associated pneumonia (106, 107, 112, 165). Patients who are colonized with MRSA, placed on a ventilator, or infected with a respiratory virus like influenza have an increased risk of acquiring MRSA pneumonia (74, 106, 112, 114, 115, 166). Patients with MRSA pneumonia may experience poor outcomes such as extended hospital stays or death (106, 112, 118, 165, 167). In particular, patients with necrotizing MRSA pneumonia have a high likelihood of dying, given the reported fatality rate of 75% (118). Organizations, such as the Infectious Diseases Society of America (IDSA), recommend agents active against MRSA for empirical treatment of patients suspected of having MRSA pneumonia (152). Vancomycin is currently one of the main antimicrobials used to treat MRSA infections (152). However, vancomycin has several potential limitations: it is not bactericidal, it does not penetrate well into lung tissue, and it can cause serious adverse effects including nephrotoxicity. In fact, some investigators have reported higher clinical success rates when treating patients who have MRSA pneumonia with alternative agents such as linezolid rather than with vancomycin (153, 154).

Specific microbial characteristics have been associated with poor outcomes in patients with MRSA pneumonia. Prior studies have linked the Panton-Valentine leukocidin (PVL) toxin with necrosis of the lung while other studies have found that *agr* was associated with fatal pulmonary infection, necrotizing pneumonia, and bacteremia (118, 119, 122, 125, 126). Some antimicrobials used to treat MRSA pneumonia may

inhibit specific microbial virulence mechanisms. For example, linezolid may decrease in vitro secretion of multiple virulence factors such as staphylococcal enterotoxins A and B, protein A, and α-hemolysin (60). Micek et al. found that three patients whose MRSA pleuropulmonary infections did not respond to vancomycin all recovered after their treatment was changed to linezolid or clindamycin, agents which inhibit exotoxin expression (158).

The current study examined host characteristics, microbial characteristics, treatment, and outcomes for patients with MRSA pneumonia to determine which factors were associated with death or with increased length of hospital stay. If we can identify factors associated with poor clinical outcomes, we may be able to improve clinical care, including antimicrobial treatment regimens, and, thereby, improve patients' outcomes.

Methods

Study design and patient population

We conducted a retrospective cohort study that included both adult and pediatric patients admitted to the University of Iowa Hospitals and Clinics (UIHC) or to the University of Maryland Medical Center (UMMC) during 2003-2010. Patients were initially identified by *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) codes for pneumonia or influenza-like illness (168). Patients were included if they had an ICD-9-CM code for pneumonia (480-488, V12.61, 997.31) and had a MRSA isolate from either a respiratory (sputum, bronchial specimen, or tracheal aspirate) culture or a blood culture banked in the clinical microbiology laboratory during their admission. Patients were excluded if they had an ICD-9-CM code for aspiration pneumonia (507) or if they had only an ICD-9-CM code for pneumonia caused by an organism other than MRSA.

A patient having multiple admissions for MRSA pneumonia was included only once. Additionally, if a patient had multiple isolates banked during the admission for pneumonia, the isolate from the first culture that grew MRSA was analyzed. Patients'

data were collected from their electronic medical record (Appendix A: chart review form). This study was approved by the institutional review board of the University of Iowa.

Variable Definitions

The primary outcomes analyzed were 30-day-all-cause in-hospital mortality and length of stay in the hospital. Mortality was defined as death occurring within the 30 days immediately after the date when the first culture that grew MRSA was obtained. Thirty-day mortality was selected since a > 30 day cutoff would include more patients who died from causes other than MRSA pneumonia. Hospital length of stay was defined as the day the first respiratory or blood culture that grew MRSA was collected until the day the patient was either discharged from the hospital or died.

Antimicrobials started during the two days before the first culture that grew MRSA was obtained and during the following five days were included in our study as treatment for the MRSA pneumonia. Patient's comorbidities were examined with the Charlson Comorbidity Index, which is calculated based on ICD-9-CM codes (169). Table 3.1 lists the categories of comorbidities that were included in the Charlson Comorbidity score and the standard weights attributed to each category. Hospital-onset infections were defined as a patient whose first positive MRSA culture was obtained greater than two days after admission to the hospital. Healthcare-associated MRSA (HA-MRSA) isolates were defined as an MRSA isolate that had the following molecular characteristics: a genetic fingerprint related to the strain USA100, SCC*mec* type II, and PVL-negative. Community-associated MRSA (CA-MRSA) isolates were defined as an MRSA isolate that had the following molecular characteristics: a genetic fingerprint related to the strain USA300, SCC*mec* type IV, and PVL-positive. Of note, investigators still classify isolates as community-associated and healthcare-associated even though the terms no longer reflect the origin (community vs. healthcare) of the isolates. For example, community-associated MRSA isolates may cause hospital-onset infections.

Laboratory Testing

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using broth dilution as described by the Clinical and Laboratory Standards Institute (170). Isolates were tested for susceptibility to tetracycline, trimethoprim-sulfamethoxazole, tigecycline, levofloxacin, linezolid, daptomycin, and vancomycin. The *S. aureus* isolate ATCC 29213 was used for quality control. Linezolid minimum inhibitory concentrations were read at 90% inhibition.

Pulsed-Field Gel Electrophoresis (PFGE)

PFGE was performed according to previously published methods (171). Chromosomal DNA was digested using the restriction enzyme *SmaI* (Sigma-Aldrich, St. Louis, MO). Banding patterns were analyzed using Bionumerics™ software (Applied Maths, Kortrijk, Belgium) and compared with the type strains USA100 to USA1200 (Figure 3.1). A similarity coefficient of 80% was used to determine genetic relatedness.

Accessory Gene Regulator (*agr*) Screening Test

agr function was examined by measuring the expression of δ-hemolysin using a β-lysin disk according to previously published methods (Figure 3.2) (172).

Panton-Valentine leukocidin (PVL)

The presence of the PVL gene was identified using a previously described polymerase chain reaction (PCR) method (156). PCR products were separated on a 1.5% SeaKem GTG agarose gel in 0.5 Tris-borate-EDTA buffer at 130V and stained with ethidium bromide (Figure 3.3).

Toxic Shock Syndrome Toxin-1(TSST-1)

TSST-1 was identified using modifications of previously published methods (156, 173). Two colonies were taken from fresh blood agar plates and suspended into 100 µl of distilled water. Amplification was performed using 10 Biolase buffer, 400 nM GTSSTR-1, 400 nM GTSSTR-2, 200 µM deoxynucleoside triphosphate, 1.5 mM MgCl2, 400 nM

GFEMAR-1, 400 nM GFEMAR-2, 1.25 U of Biolase *Taq* polymerase, and 3 µl of cells in a final volume of 50 µl. The PCR conditions were 94° C for 10 min; followed by 35 cycles of 94° C for 2 min, 57° C for 2 min, and 72° C for 1 min; and finally 72° C for 7 min. PCR products were separated on a 1.5% SeaKem GTG agarose gel in 0.5 Tris-borate-EDTA buffer at 130 V and stained with ethidium bromide (Figure 3.3).

Arginine Catabolic Mobile Element (ACME)

ACME was identified using modifications of previously published methods (133, 156). Two colonies were taken from fresh blood agar plates and suspended into 100 µl of distilled water. Amplification was performed using 10 Biolase buffer, 400 nM *arcA-1*, 400 nM *arcA-2*, 200 µM deoxynucleoside triphosphate, 1.5 mM MgCl2, 1.25 U of Biolase *Taq* polymerase, and 3 µl of cells in a final volume of 50 µl. The PCR conditions were 95° C for 10 min; followed by 35° cycles of 95° C for 20 s, 55° C for 30° s, and 72° C for 90 s; and finally 72° C for 5 min. PCR products were separated on a 1.5% SeaKem GTG agarose gel in 0.5 Tris-borate-EDTA buffer at 130 V and stained with ethidium bromide (Figure 3.3).

Staphylococcal Cassette Chromosome *mec* (SCC*mec*)

SCC*mec* typing was performed using multiplex PCR to identify the SCC*mec* cassette types I to V (156). PCR products were separated on a 1.5% SeaKem GTG agarose gel in 0.5 Tris-borate-EDTA buffer at 130V and stained with ethidium bromide (Figure 3.4).

Heterogeneous Vancomycin-Intermediate *S. aureus* (hVISA) Screening Test

Isolates were tested for hVISA using previously published methods (174). Four 10 µL 0.5 McFarland drops were placed on plates containing Brain Heart Infusion agar (Difco, Becton Dickinson and Company) with casein (Difco, Becton Dickinson and Company) and vancomycin. Plates were analyzed at 48 hours for growth. hVISA was defined as having at least one drop with ≥ 2 colonies (174).

Statistical Analysis

Bivariable analyses were conducted using either the Student t-test or the Wilcoxon Rank Sum test for continuous variables and either the chi-square test or the Fisher's exact tests for categorical variables to assess whether patient characteristics, microbial characteristics, or treatment were associated with the outcome variables (30-day mortality, length of stay). Statistical significance was defined as $P < 0.05$. Data were analyzed using SAS software (SAS Institute, Cary, NC) version 9.3. Age was dichotomized on the median (54 years).

Cox proportional hazard regression was used to perform the multivariable analyses assessing the association of various factors with 30-day mortality; hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Patients were censored if mortality occurred more than 30 days after the date the first positive MRSA respiratory or blood culture was collected, or if they were discharged from the hospital after the date the positive MRSA respiratory or blood culture was obtained. Additionally, patients were censored if they were discharged from the hospital and then died within 30 days after the date of the first positive culture. Variables were entered into the model using a manual stepwise method. Variables were examined for fit within the multivariable model if they had a $P < 0.25$ in the bivariable regression analysis and were kept in the multivariable model if they had a $P < 0.05$. The proportional hazard assumption was assessed for each variable in the final model by examining the interaction of the variable with the log of time.

Ordinal logistic regression was used to calculate odds ratios (OR) and 95% CI for the association of potential predictor variables and increased length of stay. Patients were categorized based on their length of stay: 0-3 days, 4-10 days, 11-20 days, and ≥ 21 days. Since deceased patients had the worst outcome and varying lengths of stay before death, they were placed in a separate category that was categorized as ≥ 21 days. The reference group for the analysis was 0-3 days. Variables were entered and included using the same stepwise method and criteria described above.

Potential confounders and effect modifiers were assessed for both the survival analysis and logistic regression analysis using the following methods. Variables were individually reinserted into the final model to assess for confounding. If the variable altered the regression coefficient of the variables in the final model by greater than 20%, then the variable was considered a confounder, and it was included in the final model. Potential effect modifiers were examined by creating interaction terms between the potential effect modifier and the predictor variable in the final model. If the interaction term was statistically significant ($P < 0.05$), the variable was considered an effect modifier and was included as an interaction term in the final model.

Results

Two-hundred and fifty-four MRSA isolates were identified from respiratory or blood cultures of patients who had pneumonia or influenza-like illness symptoms. Of the 254 MRSA isolates, 71 isolates were excluded because patients did not have an ICD-9-CM code for pneumonia, and four isolates were excluded because patients had pneumonia caused by organisms other than MRSA. Additionally, 48 isolates were excluded because the patients had multiple MRSA isolates banked during their admissions. Therefore, 131 patients with pneumonia and MRSA isolates were included in the study. The majority of the isolates were from respiratory cultures, including bronchial washes (15%), tracheal aspirates (4%), and sputum cultures (79%). Only 2 (2%) of the isolates were from blood cultures.

Most patients were admitted to UMMC (86%) and over half were male (63%). The median age was 54 years (range: 42-65). Approximately half of the patients were admitted to an ICU (53%), had hospital-onset MRSA pneumonia (51%), or were admitted to the same hospital during the prior year (43%). The median length of stay in the hospital was eight days (range: 3-19). Sixty percent of the patients acquired MRSA pneumonia in 2007-2009 and 25% occurred during 2009. Eight of 28 (6%) patients, who were evaluated for influenza, had positive influenza tests.

Twenty-three (18%) patients with MRSA pneumonia died. Compared with the patients who survived, the patients who died were more likely to be older than 54 years (78% vs. 41%; $P = 0.001$), were more likely to be admitted to an ICU (87% vs. 46%; $P < 0.001$), and had a shorter hospital length of stay (median: 4 vs. 9 days; $P = 0.003$; Table 3.2). In addition, three of eight (38%) patients who had positive influenza tests died. Patients who died in the hospital were more likely to have received appropriate treatment (linezolid or vancomycin) for their MRSA pneumonia than the patients who survived (83% vs. 42%; $P = 0.029$; Table 3.2). Seventy-four percent of the patients who died received vancomycin compared with 44% of the patients who survived ($P = 0.010$), and 27% of the patients who survived received a cephalosporin compared with 4% for those who died ($P = 0.020$).

The presence of specific microbial characteristics or virulence factors in the infecting organisms was not associated with mortality (Table 3.3). A higher proportion of MRSA isolates from survivors than isolates from patients who died were PVL-positive (45% vs. 30%; $P = 0.189$) or ACME-positive (44% vs. 22%; $P = 0.053$). However, MRSA with a dysfunctional *agr* was more frequently identified in patients who died (22% to 12%; $P = 0.313$). Nearly two thirds of the MRSA isolates from patients that died had a PFGE type related to USA100 and were SCC*mec* Type II and PVL-negative, which is consistent with healthcare-associated strains. In contrast, less than half of the MRSA isolates from patients who survived met the criteria for healthcare-associated strains. Compared with isolates from patients that died, a higher percentage of the MRSA isolates from patients that survived had a PFGE type related to USA300 and were SCC*mec* Type IV and PVL-positive, which is consistent with CA-MRSA strains (44% vs. 22%; $P = 0.053$). However, none of the associations between microbial characteristics and mortality reached statistical significance at the 0.05 level. Additionally, most MRSA isolates were susceptible to all antimicrobials tested except levofloxacin (7% susceptible), and all isolates were susceptible to vancomycin and linezolid (Table 3.4).

Results of the bivariable analyses for risk factors associated with mortality and excess length of stay are provided in Table 3.5. The results of the multivariable models are provided in Table 3.6. In the Cox proportional hazard model, increased age (≥ 55 years) (HR: 4.49; CI: 1.64-12.33) and ICU admission (HR: 5.25; CI: 1.52-18.21) were associated with in-hospital mortality. Additionally, a protective effect was observed for hospital-onset MRSA pneumonia (HR: 0.32; CI: 0.13-0.75). In the ordinal logistic regression model, patients with MRSA pneumonia that were admitted to an ICU (OR: 7.34; CI: 3.58-15.04), were older (≥ 55 years) (OR: 2.27; CI: 1.19-4.35), had a hospital-onset MRSA pneumonia (OR: 3.60; CI: 1.26-10.28), or received vancomycin (OR: 10.85; CI: 3.68-32.00) had an increased odds of having an extended length of stay in the hospital compared with patients that did not have these factors. However, the odds decreased in patients with hospital-onset MRSA pneumonia who also received vancomycin (OR: 1.96; CI: 0.76-5.06).

Eighty-two (63%) patients received vancomycin, linezolid, or both for their infections, and, therefore received appropriate treatment for MRSA pneumonia. Fifty-seven (70%) patients received vancomycin, 17 (21%) received linezolid, and 8 (10%) received both (Table 3.7). Most of the patients who were prescribed either vancomycin (58%) or linezolid (76%) were admitted to the ICU during their hospitalization. Additionally, the majority of patients who were prescribed linezolid (76%) had hospital-onset infections while 33% of the patients who were given vancomycin had a hospital-onset infection (Table 3.7). Patients who received linezolid had the longest length of stay with a median of 22 days (Table 3.7). However, the mortality rate was the highest in the patients who received vancomycin (28%). Many of the patients who were prescribed vancomycin were given at least one other antimicrobial. Fifty-four percent of patients given vancomycin also received piperacillin/tazobactam compared with 12% of patients receiving linezolid or 16% of patients receiving inappropriate treatment ($P < 0.001$; Table 3.7).

Among patients infected with a PVL-positive isolate, the patients who were treated with vancomycin for MRSA pneumonia had a 54% increased hazard for mortality compared with patients who were treated with another antimicrobial (HR: 1.54; CI: 0.34-6.87). Additionally, among patients infected with an *agr* dysfunctional isolate, patients with MRSA pneumonia that were treated with vancomycin were more likely to die than were patients that received another antimicrobial agent (HR: 2.44; CI: 0.27-21.91). However, neither of these associations reached statistical significance at the 0.05 level, which was probably due to the small sample size (*agr* dysfunction: N = 18, PVL-positive cohort: N = 56).

Discussion

The mortality rate for patients with MRSA pneumonia in our study is lower than the mortality rates found in many other studies, which were between 33% and 60% (175-178). We examined both hospital-onset and community-onset infections whereas many of the previous studies included only hospital-onset infections. Patients with hospital-onset MRSA pneumonia might have a high risk of mortality due to compromised immune systems caused by underlying comorbidities, medication use, or age. Their comorbidities may also compromise the patients' ability to meet the increased physiological and metabolic demands associated with pneumonia. Also, our study included only patients that died in the hospital within 30 days of their first positive MRSA respiratory or blood culture. The previous studies may have included patients that died > 30 days after the first positive culture or patients that died outside of the admitting hospital.

We identified ICU admission and older age as risk factors for mortality. Haque et al. also found a significant difference in age between patients with hospital-onset MRSA pneumonia who died compared with patients who survived (mean: 67 vs. 56 years; $P \leq 0.001$) (177). Furthermore, Haque et al. found higher APACHE II scores in patients who died compared with patients who survived (mean score: 23.6 vs. 18.8; $P \leq 0.001$) (177). A limitation to our study is that we were unable to calculate a severity of illness score.

However, admission to the ICU might be a marker for increased severity of illness in our study since severely ill patients are typically admitted to ICUs.

The results of some studies suggest that specific pathogenic characteristics of MRSA isolates causing infections are associated with poor outcomes but the results of other studies do not confirm these findings (118, 122-126, 129, 132, 179). We did not find any associations between specific microbial characteristics and increased mortality or length of stay. However, we identified an increased hazard for mortality among patients who were infected with a PVL-positive isolate and who received vancomcyin compared with patients who did not receive vancomycin, and the hazard for mortality was 2-fold higher for patients infected with an *agr* dysfunctional isolate and who received vancomycin compared with patients who did not receive vancomycin. Yet, these relationships were not statistically significant. Even though our cohort of patients with MRSA pneumonia was larger than most studies on this topic, we suspect that our sample size was too small to identify statistically significant associations between some of the microbial characteristics and poor outcomes. Additionally, we hypothesized that similarities may have existed between some of the microbial characteristics and hospital-onset infections. Therefore, we removed hospital-onset infections from the final models and reexamined each microbial characteristic within the models. However, none of the individual microbial characteristics were statistically significant at the 0.05 level when placed in the models.

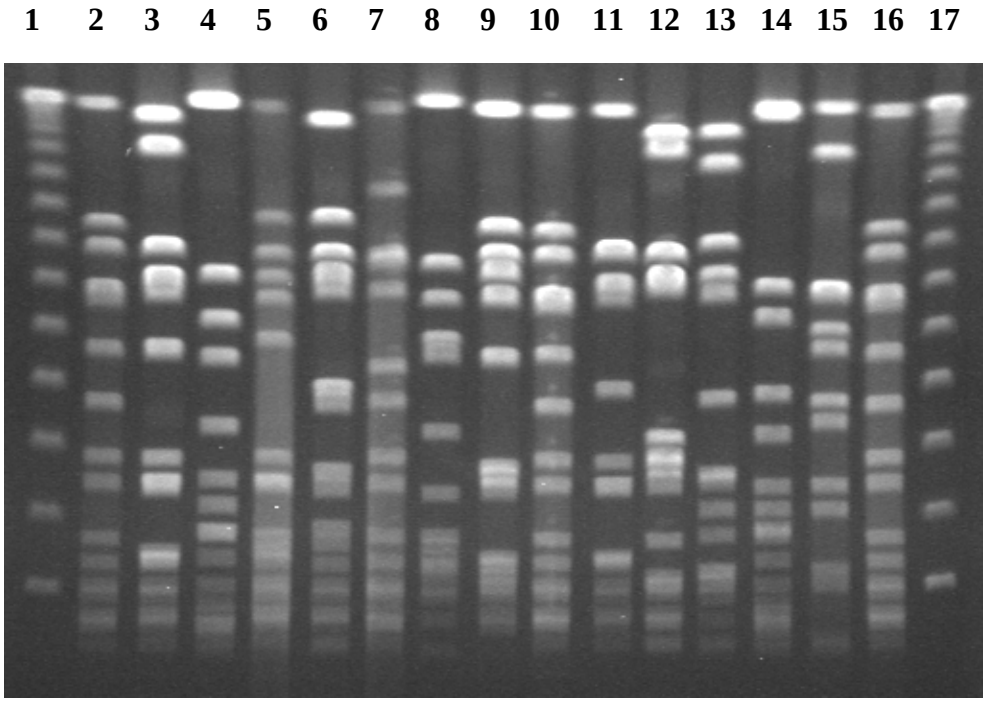
In our study, 33% of patients with MRSA pneumonia did not receive appropriate treatment for their MRSA infections. In contrast, Kallen et al. reported that 57% of patients with MRSA pneumonia did not receive empiric treatment with an agent active against MRSA (176). Additionally, researchers have postulated that inappropriate empirical antibiotic therapy is associated with higher mortality in patients with healthcare-onset pneumonia compared with patients who have community-onset pneumonia (180). We did not find an association between healthcare-onset pneumonia

and mortality, and only four (8%) of the patients receiving inappropriate therapy died. We hypothesize that the patients who received appropriate treatment for MRSA pneumonia were sicker than the patients who received inappropriate treatment. More patients that received vancomycin (58%) or linezolid (76%) were admitted to an ICU compared with patients that received neither of these drugs (45%). Additionally, the length of stay in the hospital was shorter for patients that received inappropriate therapy compared with patients that were treated with vancomycin or linezolid (6 vs. 10 vs. 22 days). However, it is also plausible that the patients receiving inappropriate therapy did not have pneumonia caused by MRSA, but they may have had either a less severe MRSA respiratory tract infection or their respiratory tracts were colonized with MRSA. Thus, these patients recovered without appropriate treatment for MRSA pneumonia, and their length of stay was shorter because they did not have a severe MRSA infection.

Our study had several limitations. First, we were unable to collect information on the details of the patients' antimicrobial treatment, such as the date the patient stopped taking the antimicrobial and the dose of the drug. Therefore, patients may have been taking an antimicrobial before the start of our treatment period. Some patients may have been prescribed vancomycin before our treatment period and were switched to linezolid during our treatment period because their respiratory tract infections did not improve which may explain the association with increased length of stay among the patients treated with linezolid. Additionally, our study suggests that vancomycin treatment may be a marker for more severe illness. The majority of patients with MRSA pneumonia that received vancomycin acquired their infection in the community (67%) and were admitted to ICUs for treatment (58%). Physicians prescribed vancomycin to treat the MRSA pneumonia, but it could be that patients died because their immune systems were overwhelmed by the infection or because the pneumonia worsened their underlying conditions, leading to organ failure and death.

In summary, MRSA pneumonia is associated with poor clinical outcomes including longer hospital length of stay and increased risk of death. ICU admission, increased age, and having a hospital-onset infection were associated with mortality, and ICU admission, increased age, and receipt of vancomycin were risk factors for increased length of stay. However, severity of illness may be an additional risk factor for poor outcomes. Surprisingly, specific molecular and virulence characteristics were not associated with increased risk of death or with long hospital length of stay. However, this finding may be due to the limited sample size. Further research is needed to identify optimal treatment for MRSA pneumonia and to assess where microbial factors or microbial factors in combination with treatment or patient factors increase the risk of death and other adverse outcomes.

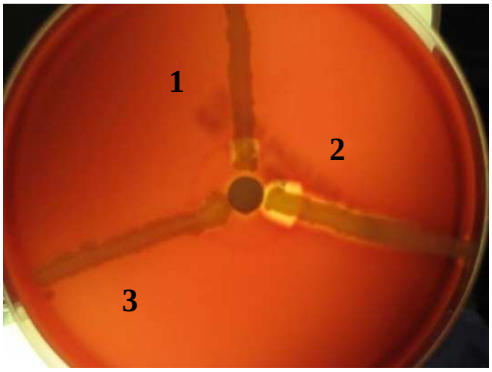
Figure 3.1: Pulsed-field gel electrophoresis (PFGE) gel of USA type strains: USA100-USA1200



Note:

Lanes 1 and 17: Molecular weight ladder
Lanes 2, 10, and 16: Control
Lane 3: USA100
Lane 4: USA200
Lane 5: USA300
Lane 6: USA400
Lane 7: USA500
Lane 8: USA600
Lane 9: USA700
Lane 11: USA800
Lane 12: USA900
Lane 13: USA1000
Lane 14: USA1100
Lane 15: USA1200

Figure 3.2: Accessory Gene Regulator (*agr*) Screening Test

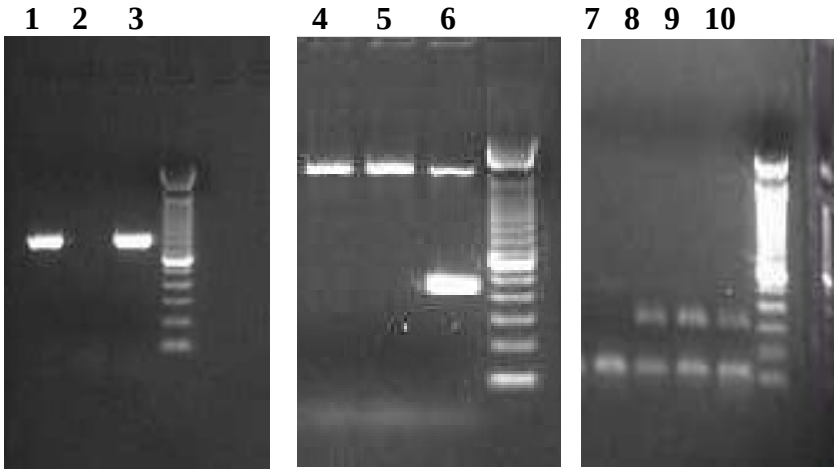


Note:

Isolates 1 and 2 display δ-hemolysin-functional *agr*

Isolate 3 displays no δ-hemolysin-dysfunction *agr*

Figure 3.3: Polymerase chain reaction products from Arginine Catabolic Mobile Element (ACME), Panton-Valentine leukocidin (PVL), and toxic shock syndrome toxin-1(TSST-1) -- isolates from patients with MRSA pneumonia



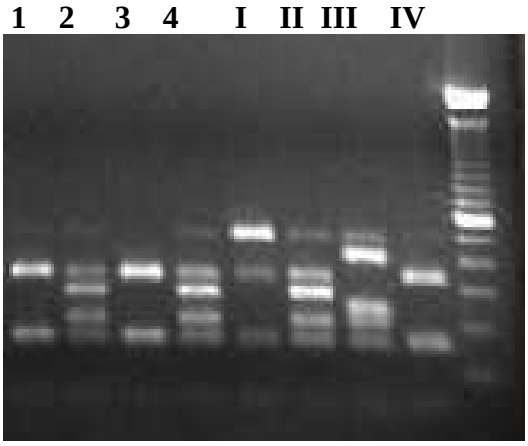
Note:

ACME:
Lanes 1 and 3: ACME positive
Lanes 2: ACME negative (absence of band at 750 bp)

PVL:
Lanes 4 and 5: PVL negative (absence of band at 433 bp)
Lane 6: PVL positive

TSST-1:
Lane 7: TSST-1 negative (absence of band at 326 bp)
Lanes 8, 9, and 10: TSST-1 positive

Figure 3.4: Polymerase chain reaction for Staphylococcal Cassette Chromosome *mec* (SCC*mec)* Types I-IV --isolates from patients with MRSA pneumonia



Note:

Lanes 1 and 3: Patient isolates type IV
Lanes 2 and 4: Patient isolates type II
Lanes 5-8: SCC*mec* type I-IV

Table 3.1: Categories and weights of the Charlson Comorbidity Index[a]

Comorbid Condition	Weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Diabetes with chronic complications	1
Hemiplegia or paraplegia	2
Renal disease	2
Any malignancy, including leukemia and lymphoma	2
Moderate or severe liver disease	2
Metastatic solid tumor	6
AIDS	6

[a] Source: Deyo, R. A., D. C. Cherkin, and M. A. Ciol. 1992. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J. Clin. Epidemiol. 45:613-619.

Table 3.2: Characteristics of patients with MRSA pneumonia who died compared with patients who survived

Characteristic	Patients who Died[a,b] N=23	Patients who Survived[b] N=108	P-value
Gender: Female (%)	12 (52)	37 (34)	0.107
Age > 54 years	18 (78)	44 (41)	0.001
Chronic obstructive pulmonary disease	8 (35)	33 (31)	0.691
Hospital admission within previous 12 months	9 (39)	47 (44)	0.699
Previous MRSA infection or colonization	6 (26)	23 (21)	0.615
Pneumonia occurring during influenza season[c]	23 (100)	100 (93)	0.349
Positive influenza test	3 (13)	5 (5)	0.146
Admitted to an intensive care unit	20 (87)	50 (46)	< 0.001
Hospital-onset infection[d]	10 (43)	57 (53)	0.418
Length of stay: median (IQR), in days[e]	4 (1-8)	9 (4-22)	0.003
Admission to discharge or death: median (IQR), in days	7 (3-14)	17 (6-34)	0.004
Charlson Comorbidity Index score: median (IQR)	2 (1-3)	1 (0-3)	0.281
Received appropriate treatment[f]	19 (83)	63 (42)	0.029
Antimicrobial prescribed			
Linezolid	3 (13)	22 (20)	0.564
Vancomycin	17 (74)	48 (44)	0.010
Macrolide	1 (4)	17 (16)	0.196
Aminoglycoside	1 (4)	10 (9)	0.688
Piperacillin/Tazobactam	10 (43)	34 (31)	0.269
Fluoroquinolone	6 (26)	27 (25)	0.913
Cephalosporin	1 (4)	29 (27)	0.020

[a] Defined as death occurring within the 30 days immediately after the date when the first respiratory or blood culture that grew MRSA was obtained.

[b] The numbers in parentheses are percentages unless otherwise specified.

[c] Defined as MRSA pneumonia occurring during October – May and anytime during 2009.

[d] Positive MRSA culture occurred > 2 days after admission.

[e] Defined as the day the first respiratory or blood culture that grew MRSA was collected until the day the patient was either discharged from the hospital or died.

[f] Prescribed vancomycin or linezolid.

Table 3.3: Microbial characteristics of MRSA isolates from patients with MRSA pneumonia who died compared with those of MRSA isolates from patients who survived

Characteristic	Isolates from Patients who Died[a,b] N=23	Isolates from Patients who Survived[b] N=108	P-value
Panton-Valentine leukocidin	7 (30)	49 (45)	0.189
SCC*mec*[c]			
Type II	15 (65)	51 (48)	0.117
Type IV	8 (35)	56 (52)	0.137
agr dysfunction[d]	5 (22)	13 (12)	0.313
Arginine Catabolic Mobile Element	5 (22)	47 (44)	0.053
Toxic Shock Syndrome Toxin-1	1 (4)	4 (4)	0.884
PFGE Type[e]			
USA100	14 (61)	47 (44)	0.130
USA300	6 (26)	50 (50)	0.075
Healthcare-associated[f]	14 (61)	46 (43)	0.110
Community-associated[g]	5 (22)	47 (44)	0.053
hVISA[h]	1 (4)	6 (6)	1.000

[a] Defined as death occurring within the 30 days immediately after the date when the first respiratory or blood culture that grew MRSA was obtained.

[b] The numbers in parentheses are percentages unless otherwise specified.

[c] Staphylococcal Cassette Chromosome *mec.*

[d] Accessory gene regulator.

[e] Pulsed-field gel electrophoresis.

[f] Strains that were related to USA100, SCCmec Type II, and PVL-negative.

[g] Strains that were related to USA300, SCCmec Type IV, and PVL-positive.

[h] Heterogeneous Vancomycin-Intermediate *S. aureus.*

Table 3.4: Susceptibility to seven antimicrobial agents of MRSA isolates from patients with MRSA pneumonia (N = 131)

Antimicrobial	**MIC[a] Range (µg/mL)**	**MIC50 (µg/mL)**	**MIC90 (µg/mL)**	**% Resistant**
Tetracycline	0.12 - > 64	0.25	4	8
Trimethoprim/Sulfamethoxazole	≤ 0.03 - 32	0.06	0.06	3
Tigecycline	0.06 - 0.5	0.06	0.12	N/A
Levofloxacin	0.25 - > 64	16	> 64	93
Linezolid	0.5 - 2	1	2	0
Vancomycin	0.5 - 1	1	1	0
Daptomycin	0.25 - 2	0.5	0.5	N/A

[a] Minimum inhibitory concentration.

Table 3.5: Bivariable analysis of patient characteristics, microbial characteristics, or treatments associated with 30-day-in-hospital mortality or increased length of stay among patients with MRSA pneumonia

	Outcome			
	Mortality[a]		Length of Stay[b]	
Factor	**Hazard Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Patient Characteristics				
Gender: Female	2.10 (0.93-4.77)	0.075	1.40 (0.75-2.62)	0.297
Age > 54 years	4.09 (1.52-11.03)	0.005	2.38 (1.28-4.43)	0.006
Chronic obstructive pulmonary disease	1.79 (0.74-4.37)	0.200	0.53 (0.27-1.02)	0.057
Previous hospital admission within past 12 months	0.93 (0.40-2.15)	0.866	0.55 (0.29-1.02)	0.056
Previous MRSA infection or colonization	1.41 (0.56-3.61)	0.468	0.83 (0.40-1.72)	0.617
Pneumonia occurring during influenza season[c]	1.58 (0.37-6.77)	0.537	0.84 (0.33-2.12)	0.710
Positive influenza test	2.53 (0.75-8.54)	0.136	2.52 (0.70-9.12)	0.159
Admitted to an ICU[d]	4.51 (1.33-15.27)	0.016	7.39 (3.70-14.76)	< 0.001
Hospital-onset infection[e]	0.57 (0.24-1.28)	0.167	1.34 (0.73-2.46)	0.349
Charlson Comorbidity Index score	1.08 (0.93-1.24)	0.547	0.97 (0.86-1.09)	0.567
Antimicrobial prescribed				
Linezolid	0.47 (0.14-1.61)	0.231	1.24 (0.58-2.69)	0.579
Vancomycin	2.87 (1.13-7.29)	0.026	2.71 (1.45-5.07)	0.002
Macrolide	0.40 (0.05-3.00)	0.373	0.25 (0.10-0.63)	0.004
Aminoglycoside	0.43 (0.06-3.19)	0.409	1.36 (0.45-4.05)	0.585
Piperacillin/Tazobactam	1.45 (0.63-3.30)	0.766	1.90 (0.99-3.64)	0.052
Fluoroquinolone	1.13 (0.45-2.88)	0.796	0.89 (0.44-1.79)	0.740
Cephalosporin	0.17 (0.02-1.26)	0.082	0.37 (0.18-0.78)	0.009
Microbial Characteristics				
Panton-Valentine leukocidin	0.62 (0.26-1.51)	0.291	0.63 (0.34-1.17)	0.142
SCC*mec*[f]				
Type II	1.41 (0.69-2.92)	0.350	1.55 (0.87-2.77)	0.134
Type IV	0.59 (0.25-1.40)	0.233	0.62 (0.34-1.15)	0.132
agr dysfunction[g]	0.63 (0.23-1.70)	0.362	0.51 (0.21-1.25)	0.140
Arginine Catabolic Mobile Element	0.43 (0.16-1.16)	0.096	0.55 (0.29-1.02)	0.059
Toxic Shock Syndrome Toxin-1	1.26 (0.17-9.36)	0.821	0.79 (0.16-3.84)	0.768
PFGE type[h]				

Table 3.5 Continued

USA100	1.64 (0.71-3.80)	0.245	1.71 (0.93-3.17)	0.085
USA300	0.49 (0.19-1.23)	0.127	0.56 (0.30-1.04)	0.067
Healthcare-associated[i]	1.72 (0.74-3.97)	0.206	1.65 (0.89-3.04)	0.112
Community-associated[j]	0.44 (0.16-1.18)	0.101	0.50 (0.27-0.94)	0.032
hVISA[k]	0.58 (0.08-4.34)	0.596	2.13 (0.55-8.30)	0.277

[a] Defined as death occurring within the 30 days immediately after the date when the first respiratory or blood culture that grew MRSA was obtained.

[b] Defined as the day the first respiratory or blood culture that grew MRSA was collected until the day the patient was either discharged from the hospital or died.

[c] Defined as pneumonia occurring during October – May and anytime during 2009.

[d] Intensive-care unit.

[e] Positive MRSA culture occurred > 2 days from admission.

[f] Staphylococcal Cassette Chromosome *mec.*

[g] Accessory gene regulator.

[h] Pulsed-field gel electrophoresis.

[i] Strains that were related to USA100, SCC*mec* Type II, and PVL-negative.

[j] Strains that were related to USA300, SCC*mec* Type IV, and PVL-positive.

[k] Heterogeneous Vancomycin-Intermediate *S. aureus.*

Table 3.6: Multivariable analysis of factors associated with either 30-day-in-hospital mortality or increased length of stay among patients with MRSA pneumonia

Outcome: Mortality[a]	**Hazard Ratio (95% CI)**	**P-value**
Age > 54 years	4.49 (1.64-12.33)	0.004
Admission to the ICU	5.25 (1.52-18.21)	0.011
Hospital-onset infection	0.32 (0.13-0.75)	0.012
Outcome: Increased Length of Stay[b]	**Odds Ratio**[c] **(95% CI)**	**P-value**
Age ≥ 55 years	2.27 (1.19-4.35)	0.013
Admission to the ICU	7.34 (3.58-15.04)	< 0.001
Hospital-onset infection	3.60 (1.26-10.28)	0.017
Receipt of vancomycin[d]		
Hospital-acquired infection	1.96 (0.76-5.06)	0.163
Community-acquired infection	10.85 (3.68-32.00)	< 0.001

[a] Defined as death occurring within the 30 days immediately after the date when the first respiratory or blood culture that grew MRSA was obtained.

[b] Defined as the day the first respiratory or blood culture that grew MRSA was collected until the day the patient was either discharged from the hospital or died.

[c] The reference group includes patients with a length of stay between 0-3 days.

[d] Type of infection was an effect modifier for receipt of vancomycin.

Table 3.7: Patient characteristics by type of antimicrobial therapy prescribed to patients with MRSA pneumonia (N=131)

Patient Characteristic[a]	**Patients who Received Vancomycin Alone N = 57**	**Patients who Received Linezolid Alone N = 17**	**Patients who Received Linezolid and Vancomycin N = 8**	**Patients who Received Inappropriate Therapy N = 49**	**P-value**
Gender - Female	22 (39)	7 (41)	3 (38)	17 (35)	0.962
Age ≥ 55 years	28 (49)	9 (53)	4 (50)	21 (43)	0.862
Chronic obstructive pulmonary disease	17 (30)	3 (18)	3 (38)	18 (37)	0.484
Renal disease	11 (19)	2 (12)	1 (13)	4 (8)	0.407
Previous hospital admission within past 12 months	28 (49)	9 (53)	3 (38)	16 (33)	0.290
Previous MRSA infection or colonization	13 (23)	4 (24)	2 (25)	10 (20)	0.959
Positive influenza test	4 (7)	0 (0)	1 (13)	3 (6)	0.568
Pneumonia occurring during influenza season	47 (82)	15 (88)	6 (75)	47 (96)	0.067
Admitted to an ICU[b]	33 (58)	13 (76)	2 (25)	22 (45)	0.044
Hospital-onset infection[c]	19 (33)	13 (76)	2 (25)	33 (67)	< 0.001
Charlson Comorbidity Index score – median (range[d])	2 (1-5)	1 (0-2)	1 (0-1)	1 (0-5)	0.221
Length of stay - median (range[d]), in days[e]	10 (4-19)	22 (8-51)	8 (5-18)	6 (2-13)	0.046
Admission to discharge or death- median (range[d]), in days	11 (5-23)	46 (9-70)	10 (5-31)	14 (5-29)	0.044

Table 3.7 Continued

30-day-in-hospital mortality[f]	16 (28)	2 (12)	1 (13)	4 (8)	0.046
Prescribed antimicrobial					
Macrolide	7 (12)	1 (6)	1 (13)	9 (18)	0.656
Aminoglycoside	8 (14)	1 (6)	0 (0)	2 (4)	0.270
Pipercillin/tazobactam	31 (54)	2 (12)	3 (38)	8 (16)	< 0.001
Fluoroquinolone	16 (28)	2 (12)	4 (50)	11 (22)	0.206
Cephalosporin	13 (23)	0 (0)	2 (25)	15 (31)	0.040

[a] The numbers in parentheses are percentages unless otherwise specified.

[b] Intensive-care unit.

[c] Positive MRSA culture occurred > 2 days from admission.

[d] Interquartile range.

[e] Day of first positive MRSA culture to day of discharge or death.

[f] Defined as death occurring within 30 days from the patient's first positive MRSA culture.

CHAPTER 4

COMPARISON OF β-LACTAMS WITH VANCOMYCIN FOR TREATMENT OF METHICILLIN-SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS* BACTEREMIA

Abstract

Background: Previous studies indicated that vancomycin is inferior to β-lactams for treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. However, it is unclear if this association is true for both empiric and definitive treatment. The primary aim of this study was to compare β-lactams with vancomycin for empiric and definitive treatment of MSSA bacteremia.

Methods: This retrospective cohort study included patients admitted to every Veteran's Affairs hospitals from 2003 to 2011 who had a positive blood culture for MSSA. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. Empiric treatment was defined as starting an antimicrobial between two days before the collection of the first blood culture until four days after the culture collection. Definitive treatment was defined as starting or remaining on treatment between 4 days after the collection of the first blood culture until 14 days after the culture was collected.

Results: There were 11,176 patients with MSSA bacteremia included in the study. In the multivariable model, patients who received empiric treatment with a β-lactam had a 19% increased mortality hazard compared with vancomycin (HR: 1.19; 95% CI: 1.004-1.421). Additionally, when stratifying by age and APACHE III score, patients who received empiric treatment with a β-lactam who were < 63 years old (HR: 1.68; 95% CI: 1.219-2.310), or who were least ill (APACHE III score < 35) (HR: 1.40; 95% CI: 1.021-1.927) were more likely to die compared with patients who received vancomycin. However, patients who received definitive treatment with a β-lactam had a 35% decreased hazards of mortality compared with patients receiving vancomycin (HR: 0.66; CI: 0.495-0.865) after controlling for other factors.

Conclusions: For patients with MSSA bacteremia, β-lactams are superior to vancomycin for definitive treatment. However, early receipt with a β-lactam may not prevent unfavorable outcomes from occurring especially among healthier patients.

Introduction

Staphylococcus aureus is a leading etiology of bacteremia within the U.S. (79, 138). *S. aureus* bacteremia can cause unfavorable outcomes such as increased length of stay in the hospital, septic shock, recurrent or persistent infections, and death (13, 50, 181). Patients infected with a methicillin-resistant strain are twice as likely to die compared with those infected with methicillin-susceptible strains (50). Vancomycin is often prescribed for patients suspected of having *S. aureus* bacteremia since it has activity against both methicillin-resistant and methicillin-susceptible strains. For a patient infected with a methicillin-susceptible strain, organizations such as the Infectious Diseases Society of America (IDSA) recommend switching therapy to a β-lactam, such as a first generation cephalosporin or an antistaphylococcal penicillin like nafcillin or oxacillin, once the isolate is known to be methicillin-susceptible (152).

Previous studies have shown that patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia who are treated with vancomycin are more likely to have a poor outcome such as recurrence, treatment failure, and death compared with patients who are treated with a β-lactam (10-13). Additionally, investigators hypothesize that delayed appropriate treatment may affect patient outcomes (159-162). Therefore, patients with MSSA bacteremia may also have improved outcomes if they receive empiric treatment with a β-lactam instead of vancomycin. The current study compared empiric treatment with β-lactams versus vancomycin and definitive treatment with β-lactams versus vancomycin among patients with MSSA bacteremia admitted to Veterans Affairs (VA) Medical Centers.

Methods

Study Design and Patient Population

We conducted a retrospective cohort study on patients admitted to acute care VA Medical Centers from 2003 to 2011. We included patients if they had one or more blood cultures that grew *S. aureus*, isolates were susceptible to either methicillin or oxacillin by antimicrobial susceptibility testing, and the patients received a β-lactam agent active against *S. aureus* or vancomycin for treatment of their bacteremia. Table 4.1 provides a list of β-lactams that have activity against *S. aureus*. We considered each admission as independent. Therefore, we included patients who had MSSA bacteremia on multiple admissions more than once in the study. We excluded patients if they did not receive either a β-lactam or vancomycin for treatment of their bacteremia. Yet, we included patients if they received another antimicrobial in addition to a β-lactam or vancomycin.

We used medical, pharmaceutical, microbiological, and demographic data from the VA Informatics and Computing Infrastructure (VINCI) for this study. The VINCI database, validated by the VA Healthcare System through the VA Information Resource Center, contains information on patients admitted to one of 140 VA Medical Centers located throughout the U.S. VINCI includes information on both in-hospital and out of hospital fatalities. The institutional review board of the University of Iowa and the Research and Development Committee of the Iowa City VA Medical Center approved this study.

Variable Definitions

We defined the primary outcome as 30-day-all-cause mortality, defined as death occurring within 30 days after the collection of the first blood culture that grew MSSA. We selected 30 day mortality for this study because > 30 days might include patients who died from causes other than MSSA bacteremia. Additionally, previous studies used 30-day mortality to examine treatment of patients with bacteremia (10, 163). Therefore, we can compare our results more accurately to previous studies. We classified patients who were discharged from their initial hospitalization, readmitted to the hospital, and then died within 30 days after the collection of the first blood culture as fatalities for this

study. Additionally, we determined that patients who were not hospitalized when the death occurred were fatalities.

We defined antimicrobial treatment as antimicrobials started during the two days before the first blood culture that grew MSSA was collected until the following 14 days after the blood culture was collected. Patients received empiric treatment if the antimicrobial was started between two days before the day the first blood culture was collected until four days after the day the blood culture was collected (Figure 4.1). Patients received definitive therapy if they started or were still taking an antimicrobial between four days after the day the first positive blood culture was collected until 14 days after the first positive blood culture was collected (Figure 4.2). We excluded patients from the empiric treatment analysis if they received empiric treatment with both β-lactam agents and vancomycin. Likewise, we excluded patients from the definitive treatment analysis if they received definitive treatment with both β-lactam agents and vancomycin. We included patients in both the empiric treatment analysis and definitive treatment analysis if they received empiric treatment with either β-lactam agents or vancomycin and treatment was changed to either a β-lactam or vancomycin for definitive treatment or if they started a β-lactam or vancomycin for empiric treatment, and remained on the same agents during the definitive therapy period.

We used the Charlson Comorbidity Index to assess comorbid conditions. This index allows investigators to calculate a comorbidity score based on ICD-9-CM codes (169). We used the modified Acute Physiology and Chronic Health Evaluation (APACHE) III score to measure the severity of illness of the patients on hospital admission (182). The APACHE III score includes the patient's age, comorbid conditions, and acute physiologic abnormalities. Table 4.2 describes the components and the points, or range of points, attributed to each component of the score. In general, patients who did not have a comorbid condition or who had a physiologic result that fell within the normal range received zero points for that component. Additionally, patients received points for

the normal range if they had missing values for any of the components within the APACHE III score. We used ICD-9-CM codes to identify chronic health conditions and to identify patients who received dialysis during their admissions and patients who had secondary infections which include pneumonia, endocarditis, and osteomyelitis.

We defined a patient with a previous MRSA infection as a patient having a culture that grew MRSA collected during a prior admission and/or having a MRSA positive culture collected during the same admission, but before the first blood culture that grew MSSA was collected. We defined a colonized patient as a patient who had a MRSA positive nasal culture collected between the admission day and the day the first blood culture that grew MSSA was collected. Of note since 2007, VA Medical Centers are required to collect MRSA nasal surveillance swabs from all admitted patients.

A patient with secondary MSSA infection had a culture from a site other than blood that was positive within the first four days of admission, but before the day the first blood culture positive for MSSA was obtained. Some patients had cultures positive for organisms other than *S. aureus* during their admissions. We defined patients as having hospital-onset bacteremia if their first blood cultures that grew MSSA were collected > 2 days after hospital admission. We defined the length of stay as the day from the first positive MSSA culture was collected until the day of discharge or death.

Statistical Analysis

We calculated frequencies for categorical variables, and median and interquartile ranges (IQR) for continuous variables. Bivariable analyses identified relationships between patient characteristics and treatment or mortality using the chi-square test or Fisher's exact test for categorical variables and the Students t-test or the Wilcoxon Rank Sum test for continuous variables. We defined statistical significance as $P < 0.05$. We analyzed data using SAS software version 9.3 (SAS Institute, Cary, NC).

We created multivariable models using Cox proportional hazard regression to examine the association between treatment with either a β-lactam or with vancomycin

and mortality. We calculated hazard ratios (HR) and 95% confidence intervals (CI) based on the models. We censored patients if death occurred > 30 days after the first positive blood culture was collected.

For the regression analyses, we performed a manual stepwise method in which variables were entered in the model one at a time if they had a $P < 0.25$ in the bivariable analysis. Variables remained in the model if they had a $P < 0.05$. We evaluated the proportional hazard assumption on the final model by assessing the interaction of each variable with the log of survival time and we stratified variables that violated the proportional hazard assumption.

Figure 4.3 provides a conceptual framework of factors that could affect treatment and mortality in patients with MSSA bacteremia. The positive and negative signs indicate the direction of the effect on either mortality or treatment. The variables evaluated in the regression analysis included: gender, age, body mass index, APACHE III score, Charlson Comorbidity Index, diabetes, renal disease, chronic heart failure, pneumonia, osteomyelitis, endocarditis, dialysis, previous MRSA infection, secondary MSSA infection, infection with another organism, MRSA nasal colonization, hospital-onset MSSA infection, and penicillin allergy. Additionally, we examined treatment with clindamycin, aminoglycosides, quinolones, macrolides, trimethoprim/sulfamethoxazole, and linezolid in models focusing on empiric treatment because these agents are not recommended for definitive treatment of MSSA infections and therefore, should be discontinued once susceptibility results are available. We retained APACHE III score and Charlson Comorbidity Index in all models regardless of statistical significance since these variables are strong predictors of mortality and may influence treatment type.

We examined confounders and effect modifiers for each model. We considered variables as confounders if their regression coefficients for treatment type were altered by more than 20%. The final model included the confounders. Statistically significant

interaction terms were identified as effect modifiers ($P < 0.05$). We created models based on the stratified effect modifier.

Results

Patients with MSSA Bacteremia

We included 11,176 patients that had at least one blood culture which grew MSSA and that were admitted to VA Medical Centers in this study. Blood cultures that grew MSSA were equally dispersed throughout the study period with 11%-12% occurring each year except 2011 (8%) (Table 4.3). The majority of the patients were male (98%), and the median age was 63 years old (IQR: 56-74). Thirty percent of the patients had a hospital-onset MSSA bacteremia. Less than half of the patients were diabetic (42%), had renal disease (20%), or had chronic heart failure (19%). The median APACHE III score was 35 points (interquartile range (IQR): 25-44), and the median Charlson Comorbidity Index was 2 points (IQR: 1-4). Eighty-one percent of the patients received a β-lactam and 76% of the patients received vancomycin at some point during treatment of their MSSA bacteremia. Eighteen percent of the patients died, and the median length of stay in the hospital was 11 days (IQR: 6-25).

Examination of Cutoff Points for Empiric vs. Definitive Treatment

To identify the most appropriate time point that separates empiric therapy from definitive therapy, we examined three cutoff points, which included three, four, and five days after the day the first culture that grew MSSA was collected. Table 4.4 describes the percent of patients who received a β-lactam or vancomycin for each cutoff day. A higher percent of patients received vancomycin as empiric treatment compared with definitive treatment regardless of the cutoff day (empiric range: 49%-60%; definitive range: 10%-11%). Furthermore, a higher proportion of patients received a β-lactam for definitive treatment versus empiric treatment for each cutoff day (empiric range: 40%-51%; definitive range: 89%-90%). Pipericillin/tazobactam (~14%) was the most common β-

lactam that patients received for empiric treatment while the majority (~60%) of the patients received cefazolin or nafcillin for definitive treatment.

The percent of patients who received empiric vancomycin decreased across the cutoff days (range: 60%-49%) while the percent of patients who received a β-lactam increased (range: 40% -51%). The proportion of patients who received definitive treatment with vancomycin (range: 10%-11%) or a β-lactam (range: 89%-90%) remained consistent over the cutoff days. We selected the primary cutoff point since a larger decline in the proportion of patients receiving definitive therapy was observed between days three and four compared with days four and five. This suggests that more clinicians are changing treatment during this time frame. Additionally, the three cutoff days had similar unadjusted hazards ratios and 95% confidence intervals for both empiric and definitive treatment (Table 4.5). Furthermore, it was feasible for the physician to receive the susceptibility results from the clinical microbiology lab four days after the culture is collected.

Characteristics of Patients Receiving Empiric Treatment with a β-lactam, Vancomycin, Both Antimicrobials, or Neither Antimicrobials

Table 4.6 describes the characteristics of patients who received empiric therapy with a β-lactam alone, vancomycin alone, either of these antimicrobials, or neither of these antimicrobials for their MSSA bacteremia. The majority of the patients received empiric treatment with both a β-lactam and vancomycin (N = 6,380) for their MSSA bacteremia. The patients who received empiric treatment with both a β-lactam and vancomycin were more likely to have an increased APACHE III score (≥ 35 points) (range: 45%-52%; $P < 001$), diabetes (range: 37%-43%; $P = 0.009$), osteomyelitis (range: 9%-12%; $P < 0.001$), and an extended length of stay in the hospital (range [median]: 7-12 days; $P < 0.001$) compared with the patients in the other three treatment groups. Many of the patients who received neither a β-lactam nor vancomycin for empiric treatment had a previous positive MRSA culture (range: 8%-18%; $P < 0.001$) or had a positive culture

with another organism (range: 50%-59%; $P < 0.001$). Additionally, the patients in this treatment group had the highest mortality rate (range: 15%-20%; $P < 0.001$) compared with the patients in the other three treatment groups.

Patients who received empiric treatment with a β-lactam were more likely to have diabetes (44% vs. 40%; $P = 0.042$), pneumonia (18% vs. 13%; $P < 001$), and another positive MSSA culture during their admission (3% vs. 1%; $P = 0.002$) compared with patients who received vancomycin. The mortality rate was slightly higher for patients who received a β-lactam compared with the patients who received vancomycin (17% vs. 15%; $P = 0.244$).

Examination of Mortality among Patients Receiving Empiric Treatment with a β-lactam vs. Vancomycin

Nineteen percent of the patients that received empiric treatment with either a β-lactam or vancomycin died. Patients who died were more likely to be at least 63 years old (70% vs. 47%; $P < 0.001$), have chronic heart failure (27% vs. 17%; $P < 0.001$), have pneumonia (24% vs. 14%; $P < 0.001$), have a culture positive for another organism (56% vs. 50%; $P = 0.015$), and have a hospital-onset infection (41% vs. 29%; $P < 001$; Table 4.7). Patients who received empiric treatment with a β-lactam had a 19% increased mortality hazard compared with patients who received vancomycin after adjusting for severity of illness, aggregate comorbidities, age, diabetes, heart disease, osteomyelitis, infections by another organism, BMI, renal disease, and additional empiric treatment with a quinolone (HR: 1.19; 95% CI: 1.00-1.42; Table 4.8). In the multivariable model, a protective effect was observed for patients who had diabetes (HR: 0.48; 95% CI: 0.40-0.58), osteomyelitis (HR: 0.32; 95% CI: 0.20-0.52), a positive culture for another organism (HR: 0.72; 95% CI: 0.61-0.86), renal disease (HR: 0.73; 95% CI: 0.58-0.92), or obesity (HR: 0.79; 95% CI: 0.54-1.15) compared with patients who did not have these characteristics. Additionally, the patients were more likely to die if they had a high APACHE III score (≥ 35) (HR: 2.75; 95% CI: 2.23-3.39), were older (≥ 63 years) (HR:

1.78; 95% CI: 1.47-2.15), had an increased Charlson Comorbidity Index (HR: 1.03; 95% CI: 1.00-1.06), had heart disease (HR:1.37; 95% CI: 1.20-1.66), received empiric treatment with a quinolone (HR: 1.17; 95% CI: 0.97-1.40), were underweight (HR: 1.50; 95% CI: 0.97-2.34), or were overweight (HR: 1.12; 95% CI: 0.81-1.56) compared with patients who did not have these characteristics.

Age ($\lambda^2 = 8.32$; $P = 0.004$), diabetes ($\lambda^2 = 4.30$; $P = 0.038$), and receiving a quinolone ($\lambda^2 = 5.11$; $P = 0.024$) had statistically significant interaction terms at the 0.05 level in the final model, and therefore, were effect modifiers for treatment type (β-lactam vs. vancomycin) (Table 4.9). Additionally, the APACHE III score violated the proportional hazard assumption (Table 4.9). When stratifying on age and APACHE III score, the patients in each category who received a β-lactam had an increased hazard of mortality compared with patients who received vancomycin. However, the patients who were < 63 years (HR: 1.68; 95% CI: 1.22-2.31) or who had an APACHE III score < 35 points (HR: 1.40; 95% CI: 1.02-1.93) had a higher hazard ratio that was statistically significant at the 0.05 level compared with the patients who were ≥ 63 years (HR: 1.02; 95% CI: 0.82-1.25) or who had an APACHE III score ≥ 35 points (HR: 1.12; 95% CI: 0.91-1.38). When stratifying on diabetes and empiric treatment with a quinolone, the observed effects differed by category. Among the patients who had diabetes, patients who were treated with a β-lactam were less likely to die compared with patients who received vancomycin (HR: 0.88; 95% CI: 0.65-1.20). However, patients who were not diabetic and who received a β-lactam were more likely to die compared with patients who were not diabetic and who received vancomycin (HR: 1.40; 95% CI: 1.12-1.70). Additionally, a protective effect was observed among the patients who received empiric treatment with a β-lactam and a quinolone compared with patients who received vancomycin and a quinolone (HR: 0.96; 95% CI: 0.70-1.32). Whereas, among the patients who did not receive empiric treatment with a quinolone, patients who received a β-lactam had a 31%

increased hazard for mortality compared with patients who received vancomycin (HR: 1.31; 95% CI: 1.06-1.62).

Characteristics of Patients Receiving Definitive Treatment with a β-lactam, Vancomycin, Both Antimicrobials, or Neither Antimicrobial

Table 4.10 describes the characteristics of patients who received definitive therapy with a β-lactam, vancomycin, either of these antimicrobials, or neither of the antimicrobials for their MSSA bacteremia. The majority of the patients received neither of these antimicrobials for definitive treatment (N = 6,374) of their MSSA bacteremia. Additionally, these patients had the highest mortality rate (range: 13%-21%; $P < 0.001$) compared with the other treatment groups. Patients who received a β-lactam were more likely to have pneumonia (18% vs. 14%; $P = 0.019$), osteomyelitis (14% vs. 7%; $P < 0.001$), and an increased length of stay in the hospital (median: 15 days vs. 10 days; $P < 0.001$) compared with the patients receiving vancomycin for definitive treatment.

Examination of Mortality among Patients Receiving Definitive Treatment with a β-lactam vs. Vancomycin

Fourteen percent of the patients who received definitive treatment with either a β-lactam or vancomycin died. Patients who died were more likely to be older (≥ 63 years) (67% vs. 47%; $P < 0.001$), have a high APACHE III score (≥ 35 years) (70% vs. 47%; $P < 0.001$), have a high comorbidity score (median: 3 vs. 2; $P < 0.001$), have chronic heart failure (27% vs. 19%; $P < 0.001$), have pneumonia (28% vs. 16%; $P < 0.001$), have a culture positive for an organism other than *S. aureus* during their admission (67% vs. 57%; $P < 0.001$), and have a hospital-onset infection (39% vs. 27%; $P < 0.001$; Table 4.11). Patients who were prescribed a β-lactam for treatment of their MSSA bloodstream infection had a 35% lower hazard of dying within 30 days compared with patients receiving vancomycin after adjusting for severity of illness, comorbidities, diabetes, heart disease, penicillin allergy, osteomyelitis, and age (HR: 0.66; CI: 0.50-0.87; Table 4.12). In the multivariable model, a protective effect was observed for patients who had diabetes

(HR: 0.50; 95% CI: 0.42-0.60), osteomyelitis (HR: 0.38; 95% CI: 0.27-0.54), and penicillin allergy (HR: 0.54; 95% CI: 0.38-0.76) compared to patients who did not have these characteristics. Additonally, the patients were more likely to die if they had a high APACHE III score (≥ 35) (HR: 2.19; 95% CI: 1.80-2.66), were older (≥ 63 years) (HR: 1.64; 95% CI: 1.38-1.95), had an increased Charlson Comorbidity Index (HR: 1.04; 95% CI: 1.00-1.07), or had heart disease (HR: 1.25; 95% CI: 1.04-1.50) compared with patients who did not have these characteristics.

Characteristics of Patients Receiving Empiric Treatment with a First Generation Cephalosporin or Antistaphylococcal Penicillin vs. Vancomycin

Table 4.13 describes the characteristics of patients who received either a first generation cephalosporin or an antistaphylococcal penicillin with patients who received vancomycin. Patients who received empiric treatment with a first generation cephalosporin or antistaphylococcal penicillin were more likely to have osteomyelitis (13% vs. 9%; $P = 0.002$) and endocarditis (6% vs. 4%; $P = 0.016$), and less likely to have renal disease (19% vs. 23%; $P = 0.015$) or a positive culture for another organism (44% vs. 52%; $P = 0.015$). The mortality rate was significantly higher for patients that received vancomycin (15% vs. 12%; $P < 0.001$).

Examination of Mortality among Patients Receiving Empiric Treatment with a First Generation Cephalosporin or Antistaphylococcal Penicillin vs. Vancomycin

Fourteen percent of the patients who received empiric treatment with a first generation cephalosporin, antistaphylococcal penicillin, or vancomycin died. The patients who died were older (≥ 63 years) (69% vs. 46%; $P < 0.001$), had a high APACHE III score (≥ 35) (69% vs. 44%; $P < 0.001$), a high Charlson Comorbidity Index (median: 3 vs. 2; $P < 0.001$), had pneumonia (21% vs. 12%; $P < 0.001$), or a hospital-onset infection (43% vs. 30%; $P < 0.001$) compared with the patients who survived (Table 4.14). Patients who received empiric treatment with either a first generation cephalosporin or an antistaphylococcal penicillin were 18% less likely to die compared with patients who

received vancomycin after adjusting for severity of illness, aggregate comorbidities, diabetes, heart disease, osteomyelitis, and age (HR: 0.82; CI: 0.64-1.05; Table 4.15)

In the multivariable model, a protective effect was observed for patients who had diabetes (HR: 0.53; 95% CI: 0.42-0.67) or osteomyelitis (HR: 0.33; 95% CI: 0.19-0.58) compared with patients who did not have these characteristics. Additionally, patients were more likely to die if they had a high APACHE III score (≥ 35) (HR: 2.33; 95% CI: 1.81-2.99), were older (≥ 63 years) (HR: 1.81; 95% CI: 1.43-2.27), had a high Charlson Comorbidity Index (HR: 1.04; 95% CI: 1.00-1.08), or had heart disease (HR: 1.39; 95% CI: 1.10-1.75) compared with patients who did not have these characteristics.

APACHE III score ($\lambda^2 = 7.27$; $P = 0.007$) and age ($\lambda^2 = 15.81$; $P < 0.001$) were effect modifiers based on their interaction terms. Therefore, these variables were stratified and separate analyses were performed for each stratum of the variable. Additionally, renal disease and receiving an empiric quinolone violated the proportional hazard assumption. Therefore, these variables were stratified and separate analyses were performed for each stratum. Among the patients who were < 63 years, the patients who received empiric treatment with a first generation cephalosporin or antistaphylococcal penicillin were more likely to die compared with patient who received vancomycin (HR: 1.52; 95% CI: 1.03-2.23). However, among the patients who were ≥ 63 years, a protective effect was observed among the patients who received empiric treatment with a first generation cephalosporin or antistaphylococcal penicillin compared with the patients who received vancomycin (HR: 0.56; 95% CI: 0.40-0.79). Among the patient who had an APACHE III score < 35 points, the patients who received empiric treatment with a first generation cephalosporin or antistaphylococcal penicillin were more likely to die compared with the patient who received vancomycin (HR: 1.27, 95% CI: 0.86-1.88). However, a protective effect was observed among the patients who had an APACHE score ≥ 35 points and who received treatment with a first generation cephalosporin or an antistaphylococcal penicillin compared with vancomycin.

In contrast, stratifying by renal disease or by receiving a quinolone for empiric treatment did not identify differing associations. Among the patients who had renal disease, patients who received a first generation cephalosporin or an ant staphylococcal penicillin were less likely to die compared with patients who received vancomycin (HR: 0.44; 95% CI: 0.22-0.86). However, a protective effect was also observed among the patients who did not have renal disease and who received a first generation cephalosporin or antistaphylococcal penicillin compared with vancomycin (HR: 0.91; 95% CI: 0.70-1.19). Among the patients who received a quinolone for empiric treatment, patients who also received a first generation cephalosporin or an antistaphylococcal penicillin were less likely to die compared with patients who received vancomycin (HR: 0.70 95% CI: 0.43-1.14), and among the patients who did not receive a quinolone for empiric treatment, the patients who also received a first generation cephalosporin or antistaphylococcal penicillin were less likely to die compared with patients who received vancomycin (HR: 0.94; 95% CI: 0.70-1.26) (Table 4.16).

Characteristics of Patients Receiving Definitive Treatment with a First Generation Cephalosporin or Antistaphylococcal Penicillin vs. Vancomycin

Table 4.17 describes the characteristics of patients who received either a first generation cephalosporin or an antistaphylococcal penicillin with patients who received vancomycin. Patients who received definitive treatment with a first generation cephalosporin or antistaphylococcal penicillin were more likely to have osteomyelitis (15% vs. 7%; $P < 0.001$), endocarditis (6% vs. 2%; $P < 0.001$), or a positive culture for another organism (55% vs. 48%; $P = 0.004$).

Examination of Mortality among Patients Receiving Definitive Treatment with a First Generation Cephalosporin or Antistaphylococcal Penicillin vs. Vancomycin

Thirteen percent of the patients who received definitive treatment with a first generation cephalosporin, an antistaphylococcal penicillin, or vancomycin died. The patients who died were older (≥ 63 years) (67% vs. 47%; $P < 0.001$), had a high

APACHE III score (≥ 35) (70% vs. 47%; $P < 0.001$), a high Charlson Comorbidity Index (median: 3 vs. 2; $P < 0.001$), had pneumonia (65% vs. 53%; $P < 0.001$), or a hospital-onset infection (38% vs. 25%; $P < 0.001$), compared with the patients that survived (Table 4.18). Patients who received definitive treatment with either a first generation cephalosporin or an antistaphylococcal penicillin were 38% less likely to die compared with patients receiving vancomycin after adjusting for severity of illness, aggregate comorbidities, diabetes, heart disease, osteomyelitis, age, and penicillin allergy (HR: 0.62; CI: 0.47-0.83; Table 4.19). In the multivariable model, a protective effect was observed for patients who had diabetes (HR: 0.51; CI: 0.41-0.63), osteomyelitis (HR: 0.41; CI: 0.28-0.62), and a penicillin allergy (HR: 0.63; CI: 0.43-0.92) compared to patients who did not have these characteristics. Additionally, the patients were more likely to die if they had a high APACHE III score (≥ 35) (HR: 2.05; CI: 1.62-2.58), were older (≥ 63 years) (HR: 1.66; CI: 1.35-2.05), had an increased Charlson Comorbidity Index (HR: 1.05; CI: 1.01-1.09), or had heart disease (HR: 1.36; CI: 1.09-1.69) compared with patients who did not have these characteristics.

Discussion

The guidelines from the IDSA indicate that patients with MSSA bacteremia should be treated with a β-lactam, such as first generation cephalosporin or antistaphylococcal penicillin, after the antimicrobial susceptibility results are available (152). Overall, the treatment our cohort of patients received was consistent with the guidelines. Approximately 90% of the patients received a β-lactam for definitive treatment. Cefazolin (~30%) and nafcillin (~34%) were the main β-lactams prescribed for definitive therapy.

In our study, β-lactam agents were associated with improved outcomes compared with vancomycin for treatment for MSSA bacteremia. Previous studies have identified improved outcomes in patients who received a β-lactam compared with vancomycin for treatment of MSSA bacteremia (10-13). Chang et al. found that patients treated with

nafcillin were less likely to have persistent bacteremia or relapse (0% vs. 19%; *P* = 0.058) compared with patients who received vancomycin for treatment of MSSA bacteremia (13). Kim et al. discovered that patients with MSSA bacteremia who were treated with vancomycin were 3-fold more likely to die than those treated with β-lactam agents (OR: 3.3; CI: 1.2-9.5) (11). Additionally, Stryjewski et al. found an association between treatment failure and receiving vancomycin for MSSA bacteremia compared with cefazolin among patients on hemodialysis (OR: 3.53; CI:1.15-13.45) (12).

Our study found that patients who were treated empirically with a β-lactam had an increased hazard of death compared with patients who were treated with vancomycin even after adjusting for confounders such as severity of illness, age, and comorbidities. Additionally, the hazard increased in patients who were younger and healthier. Schweizer et al. identified a similar effect in patients who received appropriate empiric therapy for *S. aureus* bacteremia when stratifying by severity of illness (163). Among the patients who were the least ill, the patients who received appropriate empiric therapy had a 44% increased hazard for mortality compared with the patients who received inappropriate therapy (HR:1.44; CI:0.66-3.15) (163). Additionally, Kim et al. evaluated the risk of mortality among patients admitted to the ICU with bloodstream infections compared with patients without bloodstream infections, and they found a higher relative risk estimate for patients who had the lowest severity of illness scores (APACHE II: < 20) (RR: 6.44; CI: 5.00-8.34) compared with patients who had the highest severity of illness scores (APACHE II: ≥ 20) (RR: 1.91; CI: 1.63-2.24). We hypothesized that younger, healthier patients might have an enhanced immunologic response to the bactericidal effect of the treatment. Therefore, antimicrobial treatment with a β-lactam, which is bactericidal, may harm the healthier patients instead of improving their outcome.

Even though we found an increased hazard of mortality for empiric treatment with β-lactams, a protective effect was identified when we examined only the first generation cephalosporins and antistaphylococcal penicillins versus vancomycin. Furthermore, a

similar effect was observed when we examined definitive treatment with first generation cephalosporins and antistaphylococcal penicillins compared with vancomycin. Schweizer et al. also found a protective effect for patients treated with nafcillin or cefazolin versus vancomycin (10). They reported a 79% lower mortality hazard for patients with MSSA bacteremia who received nafcillin or cefazolin compared with vancomycin (10). Additionally, patients with MSSA bacteremia who initially received vancomycin and were switched to a β-lactam had a 69% lower mortality hazard compared with patients treated only with vancomycin (10).

Additionally, a few characteristics differed between the patients who received empiric treatment with any β-lactam compared with the patients who received empiric treatment with an antistaphylococcal penicillin or first generation cephalosporin. For example, a higher proportion of patients that received any β-lactam were older (≥ 63 years) (51% vs. 46%), had a high APACHE III score (≥ 35 points) (49% vs. 45%), had pneumonia (18% vs. 12%), or had a culture positive for an organism other than *S. aureus* (50% vs. 44%) compared with patients who received a first generation cephalosporin or antistaphylococcal penicillin. Furthermore, the multivariable model that examined treatment with any β-lactams vs. vancomycin adjusted for more variables (infection with another organism, renal disease, receiving an empiric quinolone, and BMI) compared with the multivariable model that examined treatment with an antistaphylococcal penicillin or a first generation cephalosporin compared with vancomycin. On the other hand, patient characteristics did not differ substantially between the patients who received definitive treatment with any β-lactam compared with patients who were treated with a first generation cephalosporin or an antistaphylococcal penicillin.

When one performs a comparative effectiveness analysis, one must consider confounding by indication (183, 184). We attempted to control for confounding by indication within our analysis, but we may not have eliminated its effect completely. For example, 26% of the patients who received definitive treatment with vancomycin had a

penicillin allergy. However, it is unclear why the remaining patients were treated initially with vancomycin or why they remained on vancomycin after the physicians received the susceptibility results. These patients may have been severely ill, may have had multiple comorbidities, or may have had other severe infections. We tried to account for differences between the two treatment groups by incorporating a severity of illness measure, an aggregate comorbidity score, and a variable that included infections by organisms other than *S. aureus* within our survival models.

For our study, we used a cutoff day to define empiric and definitive treatment instead of examining each patient's record to identify the day a physician changed the treatment. Therefore, we may have introduced biases when we analyzed empiric and definitive treatment. For example, patients who died or were discharged less than 4 days after the first blood culture that grew MSSA was collected were not included in the definitive analysis. Therefore, patients who were extremely ill (died) or who were least ill (discharged) probably were not included in the definitive analysis. Similarly, severely ill patients may have been excluded from the empiric and definitive analyses because they may have died before receiving treatment with β-lactams or vancomycin. Additionally, we did not examine empiric treatment in the definitive treatment analysis. Therefore, the association may be affected by patients who received empiric treatment with vancomycin and definitive treatment with β-lactams.

This study has several potential limitations. First, the results may not be generalizable to all patient populations since the patients in this study were predominantly male and admitted to a VA Medical Center. However, females comprised 2% of the study population, and gender was not associated with treatment type or mortality. Second, the cause of mortality was not collected for the deceased patients. Therefore, some patients may have died from an illness or comorbidity other than MSSA bacteremia within the 30-day period. Additionally, information regarding admission to an ICU, having an intravascular device such as a central-venous catheter, or having

undergone a surgical procedure was not available. However, severity of illness may be a marker for ICU admission since severely ill patients are typically admitted to ICUs. Additionally, intravascular devices may affect the association between treatment groups. Worse outcomes have been reported for patients with bloodstream infections that originated from intravascular devices, especially if the devices were not removed (185). Therefore, some of the patients may have worse outcomes because their central venous catheters were not removed and not due to the antimicrobials used to treat their infections.

Another limitation is that information on microbial characteristics or the minimum inhibitory concentration values were not available. MSSA strain types may have differed among the two treatment groups, which may have affected the patients' risk of death. Additionally, investigators have reported poor outcomes among patients who were infected with *S. aureus* strains that had elevated vancomycin minimum inhibitory concentrations (186-188). Holmes et al. identified a 2.5-fold increased odds of mortality for bacteremic patients infected with *S. aureus* strains that had an elevated vancomycin minimum inhibitory concentration values (E-test: >1.5 mg/L) compared with patients infected with strains that had lower minimum inhibitory concentration values (OR: 2.59; CI: 1.49-4.51) (186). Furthermore, this association remained when the investigators examined only patients with MSSA bacteremia who were treated with flucloxacillin (P = 0.001) (186).

In addition, some patient characteristics were incorporated in multiple variables within the final models. Therefore, the coefficients for these characteristics must be interpreted in this light. For example, age was presented as an independent variable, but it was also incorporated in the APACHE III score. Thus, the coefficient for the age variable must be interpreted as the effect of age over and above its effect as part of with the APACHE III score. Similarly, comorbidities, such as diabetes, were presented in the final model as independent variables, and they were incorporated in the APACHE III score

and in the Charlson Comorbidity Index. Thus the coefficient for diabetes, for example, must be interpreted as the effect after adjustment for aggregate comorbidity.

The IDSA recommends β-lactams, such as a first generation cephalosporin or an antistaphylococcal penicillin, for treatment of MSSA bacteremia. However, investigators have not determined if delayed treatment with a β-lactam increases the risk of death. We found an increased hazard of mortality for patients with MSSA bacteremia who received empiric treatment with a β-lactam compared with vancomycin, but we found a protective effect for definitive treatment with a β-lactam compared with vancomycin. Additionally, we found an association between patients who received treatment with a first generation cephalosporin or with an antistaphylococcal penicillin and a decreased hazard of death. Our study supports the IDSA guidelines that physicians should treat patients that have laboratory confirmed MSSA bacteremia with a first generation cephalosporin or an antistaphylococcal penicillin instead of vancomycin.

Figure 4.1: Time-frame for receiving empiric treatment

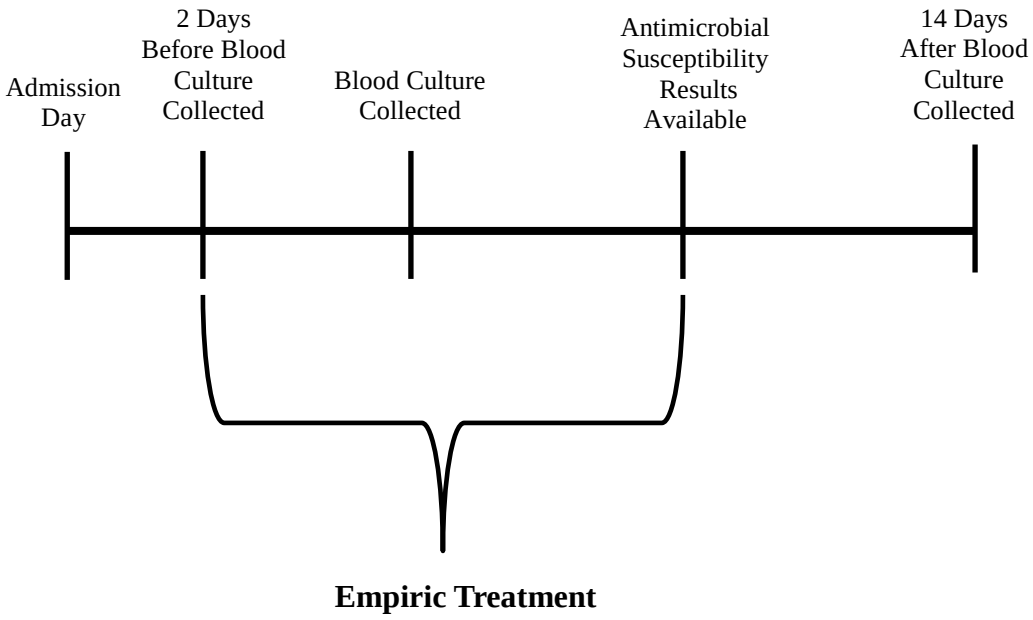


Figure 4.2: Time-frame for receiving definitive treatment

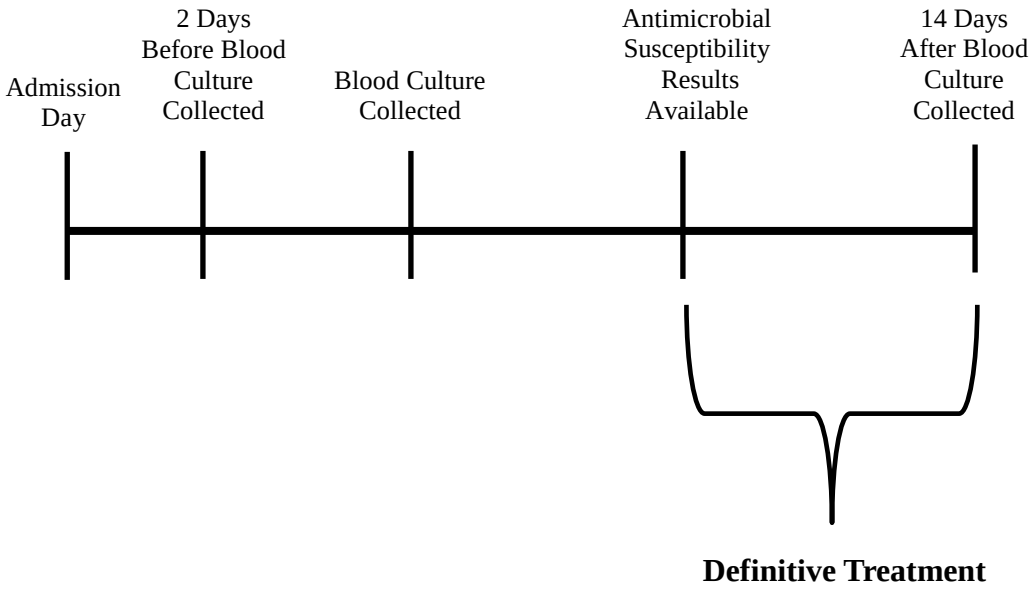


Figure 4.3: Conceptual framework

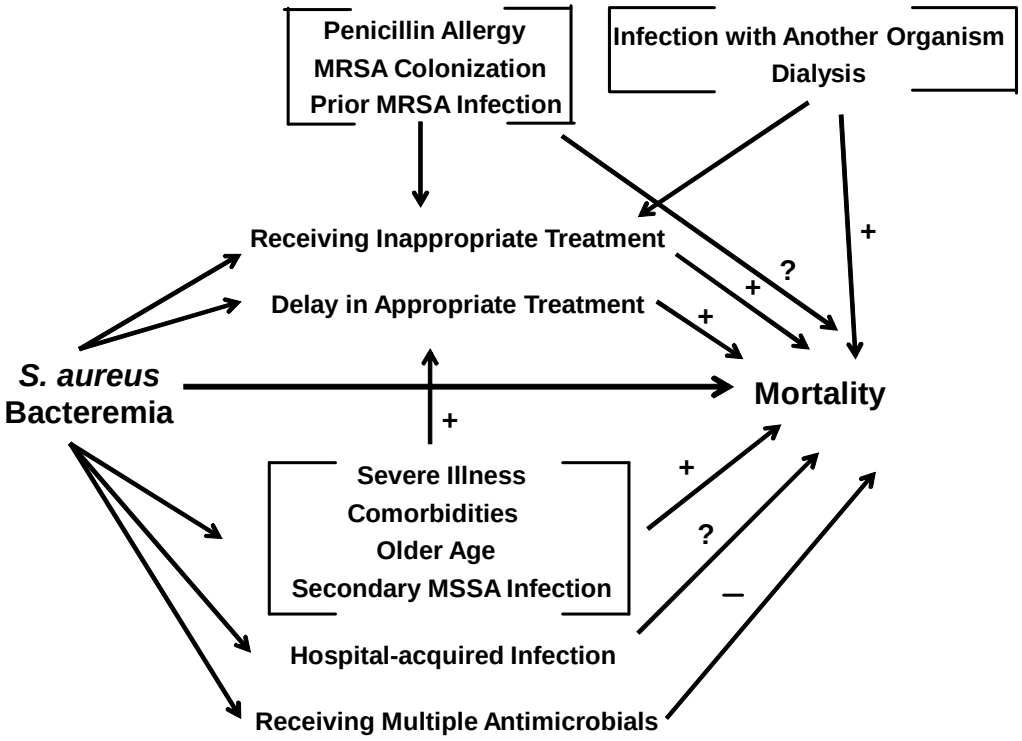


Table 4.1: β-lactams that have activity against *S. aureus*

Class of β-lactam	Antimicrobials
Antistaphylococcal penicillins	nafcillin, oxacillin
First generation cephalosporins	cephalexin, cefazolin, cefradine
Second generation cephalosporins	cefaclor, cefotetan, cefoxitin, cefprozil, cefuroxime
Third generation cephalosporins	cefdinir, cefixime, cefotaxime, cefpodoxime, ceftibuten, ceftizoxime, ceftriaxone, ceftazidime
Fourth generation cephalosporins	cefepime
Fifth generation cephalosporins	ceftaroline
Carbapenems	imipenem/cilastatin, ertapenem, doripenem, meropenem
β-lactamase inhibitors	amoxicillin-clavulanate, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam

Table 4.2: Components of the modified Acute Physiology and Chronic Health Evaluation (APACHE) III score[a]

Components of Modified APACHE III	Assigned Points
Age[b]	0-24
Comorbid conditions[c]	
AIDS	23
Hepatic Failure	16
Lymphoma	13
Metastatic cancer	11
Leukemia/multiple myeloma	10
Immunosuppression	10
Cirrhosis	4
Acute physiologic abnormalities[d]	
Pulse rate	0-17
Mean blood pressure	0-23
Temperature	0-28
Respiratory rate	0-18
Partial pressure of oxygen	0-15
Hematocrit	0-3
White blood cell count	0-19
Creatinine	0-7
Blood urea nitrogen	0-12
Sodium	0-4
Albumin	0-11
Bilirubin	0-16
Glucose	0-9

[a] Source: Knaus, W. A., D. P. Wagner, E. A. Draper, J. E. Zimmerman, M. Bergner, P. G. Bastos, C. A. Sirio, D. J. Murphy, T. Lotring, and A. Damiano. 1991. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 100:1619-1636.

[b] Patients who are $\leq$ 44 years old receive zero points whereas patients who are $\geq$ 85 years receive 24 points.

[c] Patients without the comorbid condition receive zero points whereas patients with the condition receive the points provided in the column.

[d] Patients within the normal range of an acute physiologic test receive zero points whereas patients farthest away from the normal range receive the highest points.

Table 4.3: The number of patients with and MSSA bacteremia by year of positive blood culture (N = 11,176)

Year	**N (%)**
2003	1,332 (12)
2004	1,372 (12)
2005	1,322 (12)
2006	1324 (12)
2007	1,262 (11)
2008	1,240 (11)
2009	1,219 (11)
2010	1,190 (11)
2011	916 (8)

Table 4.4: The number of patients with MSSA bacteremia who received empiric or definitive treatment with a β-lactam or vancomycin by treatment cutoff day (N=11,176)[a]

	Empiric Treatment[b]			**Definitive Treatment[c]**		
Antimicrobial	**Cutoff: 3 days N=4,015 (%)**	**Cutoff: 4 days N= 3,481 (%)**	**Cutoff: 5 days N= 3,155 (%)**	**Cutoff: 3 days N=5,617 (%)**	**Cutoff: 4 days N= 4,401 (%)**	**Cutoff: 5 days N=3,285 (%)**
Vancomycin	2,436 (60)	1,912 (55)	1,547 (49)	586 (10)	437 (10)	348(11)
β-lactams	1,579 (40)	1,569 (45)	1,608 (51)	5,031 (90)	3,964 (90)	2,937 (89)
Types of β-lactams						
Cephalexin	39 (1)	43 (1)	47 (1)	202 (4)	180 (4)	162 (5)
Cefazolin	236 (6)	283 (8)	321 (10)	1,583 (28)	1,272 (29)	942 (29)
Cephradine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cefaclor	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)
Cefotetan	5 (<1)	5 (<1)	5 (<1)	2 (<1)	2 <1)	2 (<1)
Cefoxitin	1 (<1)	1 (<1)	1 (<1)	10 (<1)	9 (<1)	6 (<1)
Cefprozil	0(0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Cefuroxime	8 (<1)	9 (<1)	9 (<1)	17 (<1)	20 (<1)	15 (<1)
Cefdinir	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cefixime	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)
Cefotaxime	17 (<1)	18 (1)	18 (1)	28 (<1)	28 (1)	21 (1)
Cefpodoxime	3 (<1)	4 (<1)	7 (<1)	25 (<1)	21 (<1)	15 (<1)
Ceftibuten	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ceftrizoxime	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Ceftriaxone	334 (8)	315 (9)	318 (10)	494 (9)	424 (10)	353 (11)
Ceftazidime	33 (1)	32 (1)	36 (1)	84 (1)	76 (2)	64 (2)
Cefepime	82 (2)	82 (2)	82 (3)	221 (4)	197 (4)	180 (5)
Ceftraroline	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	2 (<1)
Nafcillin	215 (5)	300 (9)	371 (12)	2,302 (34)	1,503 (34)	898 (27)
Oxacillin	71 (2)	105 (3)	128 (4)	555 (10)	389 (9)	235 (7)
Imipenem	24 (6)	25 (1)	24 (1)	98 (2)	87 (2)	77 (2)
Ertapenem	13 (<1)	11 (<1)	14 (<1)	75 (1)	73 (2)	59 (2)

Table 4.4 Continued

Doripenem	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Amp/sul[d]	177 (4)	168 (5)	175 (6)	233 (4)	178 (4)	123 (4)
Amox/clav[e]	34 (1)	47(1)	59 (2)	229 (4)	191 (4)	153 (5)
Ticar/clav[f]	43 (1)	41 (1)	38 (1)	26 (<1)	19 (<1)	19 (1)
Pip/tazo[g]	550 (14)	501 (14)	482 (15)	459 (8)	377 (9)	308 (9)

[a] Treatment cutoff is defined as the number of days after the day the first blood culture that grew MSSA was collected.

[b] Empiric treatment is defined as starting an antimicrobial before the cutoff day.

[c] Definitive treatment is defined as starting or remaining on an antimicrobial on or after the cutoff day.

[d] Ampicillin-sulbactam.

[e] Amoxicillin-clavulanate.

[f] Ticarcillin-clavulanate.

[g] Piperacillin-tazobactam.

Table 4.5: Unadjusted survival regression models comparing patients with MSSA bacteremia who received empiric treatment with a β-lactam versus patients who received vancomycin by cutoff day[a]

Treatment Type	Cutoff Day	Hazard Ratio (95% CI)	P-value
Empiric[b]			
	3	1.21 (1.03-1.42)	0.0224
	4	1.13 (0.95-1.33)	0.1691
	5	1.03 (0.86-1.22)	0.777
Definitive[c]			
	3	0.82 (0.58-1.15)	0.246
	4	0.67 (0.51-0.88)	0.004
	5	1.14 (0.58-1.15)	0.670

[a] Treatment cutoff is defined as the number of days after the day the first blood culture that grew MSSA was collected.

[b] Empiric treatment is defined as starting an antimicrobial before the cutoff day.

[c] Definitive treatment is defined as starting or remaining on an antimicrobial on or after the cutoff day.

Table 4.6: Characteristics of patients with MSSA bacteremia who received empiric treatment with a β-lactam alone, vancomycin alone, both antimicrobials, or neither of the antimicrobials (N = 11,176)[a]

Characteristic	Received β-lactams Alone N=1,569[b]	Received Vancomycin Alone N=1,912	Received Both[c] N=6,380	Received Neither[d] N=1,315	P-value
Gender	1,544 (98)	1,863 (97)	6,239 (98)	1,278 (97)	0.119
Age: ≥ 63 years	803 (51)	969 (51)	3,204 (50)	715 (54)	0.055
Body Mass Index					0.288
Underweight	501 (3)	51 (3)	167 (3)	49 (4)	
Normal	221 (14)	263 (14)	824 (13)	175 (13)	
Overweight	202 (13)	278 (15)	862 (14)	166 (13)	
Obese	227 (14)	255 (13)	916 (24)	166 (13)	
Unknown	869 (55)	1,065 (56)	3,611 (57)	759 (58)	
APACHE III Score: score ≥ 35	766 (49)	913 (48)	3,343 (52)	589 (45)	< 0.001
Charlson Comorbidity Index: median (range[e]) score	2 (1-3)	2 (1-4)	2 (1-4)	2 (1-4)	0.094
Diabetes	683 (44)	767 (40)	2,713 (43)	490 (37)	0.009
Renal disease	240 (15)	442 (23)	1,348 (21)	245 (19)	< 0.001
Chronic heart failure	273 (17)	359 (19)	1,207 (19)	266 (20)	0.282
Other infections					
Pneumonia	282 (18)	251 (13)	1,088 (17)	244 (19)	< 0.001
Osteomyelitis	163 (10)	163 (9)	765 (12)	113 (9)	<0.001
Endocarditis	60 (4)	75 (4)	346 (5)	30 (2)	< 0.001
Dialysis	13 (1)	4 (3)	84 (1)	13 (1)	0.119
Previous positive MRSA culture	128 (8)	195 (10)	483 (8)	238 (18)	< 0.001
Secondary MSSA infection	44 (3)	25 (1)	94 (1)	36 (3)	< 0.001
Positive culture for an organism other than *Staphylococcus aureus* during admission	782 (50)	999 (52)	3,581 (56)	7,811 (59)	< 0.001
Positive MRSA nasal culture	20 (1)	25 (1)	53 (1)	32 (2)	< 0.001
Hospital-onset infection[f]	477 (30)	594 (31)	1,560 (24)	672 (51)	< 0.001
Penicillin allergy	92 (6)	1,343 (18)	504 (8)	151 (11)	< 0.001

Table 4.6 Continued

Other empiric antimicrobials					
Clindamycin	88 (6)	160 (8)	320 (5)	72 (5)	< 0.001
Aminoglycosides	111 (7)	255 (13)	684 (11)	67 (5)	< 0.001
Quinolones	322 (21)	720 (38)	4,938 (23)	338 (26)	< 0.001
Macrolides	150 (10)	64 (3)	405 (6)	26 (2)	< 0.001
Trim/Sulfa[g]	58 (4)	74 (4)	131 (2)	36 (3)	< 0.001
Linezolid	51 (3)	14 (1)	71 (1)	34 (3)	< 0.001
Length of stay in the hospital: median (range[e)] days[h]	10 (5-24)	10 (5-22)	12 (7-26)	7 (2-31)	< 0.001
30-day mortality[i]	259 (17)	288 (15)	1,211 (19)	267 (20)	< 0.001

[a] Empiric treatment is defined as starting an antimicrobial between two days before the date of the first positive MSSA blood culture until four days after the first positive blood culture.

[b] The numbers in parentheses are percentages unless otherwise specified.

[c] Patients received empiric treatment with vancomycin and a β-lactam.

[d] Patients received empiric treatment that did not include vancomycin or a β-lactam.

[e] Interquartile range.

[f] Positive MSSA culture occurred > 2 days after admission.

[g] Trimethoprim/sulfamethoxazole.

[h] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

[i] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained.

Table 4.7: Characteristics of patients who received empiric treatment with a β-lactam or vancomycin for their MSSA bacteremia who died compared with patients who survived[a]

Characteristic	Patients who Died[b, c] N=547	Patients who Survived N=2,934	P-value
Gender	536 (98)	287 (98)	0.839
Age: ≥ 63 years	384 (70)	1,388 (47)	< 0.001
Body Mass Index			< 0.001
Underweight	27 (5)	74 (3)	
Normal	74 (14)	410 (14)	
Overweight	72 (13)	408 (14)	
Obese	44 (8)	438 (15)	
Unknown	330 (60)	1,604 (55)	
APACHE III Score: score ≥ 35	385 (70)	1,294 (44)	< 0.001
Charlson Comorbidity Index: median (range[d]) score	2 (1-4)	2 (1-3)	< 0.001
Diabetes	170 (31)	1,280 (44)	< 0.001
Renal disease	98 (18)	584 (20)	0.282
Chronic heart failure	145 (27)	487 (17)	< 0.001
Other infections			
Pneumonia	130 (24)	403 (14)	< 0.001
Osteomyelitis	17 (3)	309 (11)	< 0.001
Endocarditis	25 (5)	110 (4)	0.361
Dialysis	4 (1)	4 (1)	0.205
Previous positive MRSA culture	38 (7)	285 (10)	0.041
Secondary MSSA infection	16 (3)	53 (2)	0.085
Positive culture for an organism other than *Staphylococcus aureus* during admission	306 (56)	1475 (50)	0.015
Positive MRSA nasal culture	8 (1)	37 (1)	0.702
Hospital-onset infection[e]	222 (41)	849 (29)	< 0.001
Penicillin allergy	59 (11)	376 (13)	0.188
Other empirical antimicrobials			
Clindamycin	35 (6)	213 (7)	0.472
Aminoglycosides	59 (11)	307 (10)	0.821
Quinolones	195 (36)	847 (29)	0.002
Macrolides	32 (6)	182 (6)	0.752
Trim/Sulfa[f]	18 (3)	114 (4)	0.504
Linezolid	12 (2)	53 (2)	0.539
Length of stay in the hospital: median (range[e]) days[g]	7 (2-13)	11 (6-27)	< 0.001

[a] Empiric treatment is defined as starting an antimicrobial between two days before the day of the first blood culture that grew MSSA was collected until four days after the first positive blood culture.

[b] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained

Table 4.7 Continued

[c] The numbers in parentheses are percentages unless otherwise specified.

[d] Interquartile range.

[e] Positive MSSA culture occurred > 2 days after admission.

[f] Trimethoprim/sulfamethoxazole.

[g] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

Table 4.8: Survival regression models comparing patients with MSSA bacteremia who received empiric treatment with a β-lactam versus patients who received vancomycin (N=3,481)[a]

Model	Variable	Hazard Ratio (95% CI)	P-value
Unadjusted	β-lactam vs. vancomycin	1.13 (0.95-1.33)	0.169
Adjusted[b]	β-lactam vs. vancomycin	1.19 (1.00-1.42)	0.045
	APACHE III Score[c]	2.75 (2.23-3.39)	< 0.001
	Charlson Comorbidity Index	1.03 (1.00-1.06)	0.085
	Age[d]	1.78 (1.47-2.15)	< 0.001
	Diabetes	0.48 (0.40-0.58)	< 0.001
	Heart disease	1.37 (1.20-1.66)	0.002
	Osteomyelitis	0.32 (0.20-0.52)	< 0.001
	Infection by another organism[e]	0.72 (0.61-0.86)	< 0.001
	Renal disease	0.73 (0.58-0.92)	0.008
	Empiric quinolone	1.17 (0.97-1.40)	0.099
	Body Mass Index		
	Underweight	1.50 (0.97-2.34)	0.071
	Normal	Reference	
	Overweight	1.12 (0.81-1.56)	0.480
	Obese	0.79 (0.54-1.15)	0.213
	Unknown	1.32 (1.03-1.70)	0.031

[a] Empiric treatment is defined as starting an antimicrobial between two days before the date of the first positive blood culture until four days after the first positive blood culture.

[b] APACHE III Score and Charlson Comorbidity Index were forced in the model.

[c] Reference is < 35 points.

[d] Reference is < 63 years old.

[e] Defined as having a culture positive for an organism other than *S. aureus* during admission.

Table 4.9: Survival regression models comparing patients with MSSA bacteremia who received empiric treatment with a β-lactam versus patients who received vancomycin stratified by age, APACHE III score, diabetes, and empiric treatment with a quinolone (N=3,481)[a]

	Stratified Variable							
	Age[b]		**APACHE III Score[c]**		**Diabetes[b]**		**Empiric Quinolone[b]**	
	≥ 63 years	**< 63 year**	**≥ 35 points**	**< 35 points**	**Yes**	**No**	**Yes**	**No**
Variables in Model[d]	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
β-lactam vs. vancomycin	1.02 (0.82-1.25)	1.68 (1.22-2.31)	1.12 (0.91-1.38)	1.40 (1.02-1.93)	0.88 (0.65-1.20)	1.38 (1.12-1.70)	0.96 (0.70-1.32)	1.31 (1.06-1.62)
APACHE III Score[e]	2.55 (1.98-3.28)	3.00 (2.08-4.33)	_____	_____	2.22 (1.41-3.49)	2.94 (2.32-3.73)	2.61 (1.85-3.70)	2.80 (2.16-3.63)
Charlson Comorbidity Index	1.02 (0.98-1.06)	1.05 (0.99-1.11)	1.02 (0.98-1.05)	1.08 (0.97-1.20)	1.05 (0.99-1.11)	1.02 (0.98-1.06)	1.02 (0.96-1.08)	1.03 (0.99-1.07)
Age[f]	_____	_____	1.66 (1.31-2.10)	1.99 (1.43-2.77)	1.92 (1.35-2.73)	1.74 (1.38-2.19)	1.89 (1.36-2.64)	1.78 (1.40-2.25)
Diabetes	0.51 (0.40-0.64)	0.46 (0.32-0.66)	0.46 (0.38-0.57)	0.53 (0.33-0.84)	_____	_____	0.47 (0.34-0.65)	0.49 (0.39-0.62)
Heart disease	1.35 (1.08-1.69)	1.45 (0.92-2.29)	1.32 (1.04-1.68)	1.41 (0.96-2.05)	1.33 (0.95-1.86)	1.39 (1.09-1.78)	1.20 (0.85-1.71)	1.45 (1.14-1.85)

Table 4.9 Continued

Osteomyelitis	0.41 (0.24-0.72)	0.19 (0.07-0.53)	0.32 (0.18-0.59)	0.33 (0.14-0.75)	0.30 (0.15-0.59)	0.36 (0.18-0.73)	0.41 (0.18-0.93)	0.28 (0.16-0.52)
Second infection by another organism[g]	0.69 (0.56-0.85)	0.81 (0.59-1.11)	0.61 (0.50-0.75)	1.07 (0.77-1.49)	0.68 (0.50-0.94)	0.74 (0.60-0.92)	0.67 (0.50-0.90)	0.76 (0.61-0.94)
Renal disease	0.80 (0.61-1.04)	0.57 (0.34-0.94)	0.76 (0.58-0.98)	0.61 (0.34-1.09)	0.79 (0.55-1.14)	0.69 (0.50-0.93)	0.83 (0.54-1.26)	0.70 (0.53-0.93)
Body Mass Index[h]								
Underweight	1.45 (0.87-2.43)	1.69 (0.69-4.12)	1.44 (0.84-2.49)	1.57 (0.72-3.42)	1.96 (0.79-4.90)	1.42 (0.85-2.36)	2.23 (1.13-4.40)	1.20 (0.67-2.16)
Overweight	1.01 (0.70-1.48)	1.49 (0.78-2.85)	1.18 (0.81-1.72)	1.05 (0.54-2.02)	1.21 (0.69-2.11)	1.07 (0.71-1.60)	1.26 (0.76-2.11)	1.03 (0.68-1.58)
Obese	0.59 (0.36-0.97)	1.19 (0.62-2.28)	0.69 (0.44-1.08)	1.09 (0.55-2.18)	0.57 (0.29-1.10)	0.96 (0.61-1.52)	0.64 (0.33-1.21)	0.88 (0.55-1.40)
Unknown	1.29 (0.96-1.72)	1.49 (0.88-2.54)	1.34 (1.00-1.80)	1.31 (0.79-2.17)	1.11 (0.69-1.77)	1.43 (1.05-1.93)	1.19 (0.79-1.79)	1.39 (1.01-1.93)
Empiric quinolone	1.14 (0.92-1.41)	1.23 (0.87-1.74)	1.13 (0.91-1.41)	1.21 (0.86-1.70)	1.05 (0.75-1.45)	1.23 (0.99-1.53)	_____	_____

Table 4.9 Continued

[a] Empiric treatment is defined as starting an antimicrobial between two days before the day the first blood culture that grew MSSA was collected until four days after the first blood culture that grew MSSA was collected.

[b] Receiving empiric quinolone, diabetes, and age were effect modifiers

[c] APACHE III score score violated the proportional hazard assumption.

[d] APACHE III Score and Charlson Comorbidity Index were forced in the model.

[e] Reference is < 35 points.

[f] Reference is < 63 years old.

[g] Defined as having a culture positive for an organism other than *S. aureus* during the admission.

[h] Reference is normal.

Table 4.10: Characteristics of patients with MSSA bacteremia who received definitive treatment with a β-lactam alone, vancomycin alone, both antimicrobials, or neither of the antimicrobials (N=11,176)[a]

Characteristic	Received a β-lactam Alone N=3,964[b]	Received Vancomycin Alone N=437	Received Both[c] N=401	Received Neither[d] N=6,374	P-value
Gender	3,881 (98)	420 (96)	394 (98)	6,229 (98)	0.100
Age : ≥ 63 years	1,995 (50)	213 (49)	206 (51)	3,277 (51)	0.565
Body Mass Index					0.075
Underweight	112 (3)	14 (3)	13 (3)	178 (3)	
Normal	531 (13)	64 (15)	64 (16)	824 (13)	
Overweight	577 (15)	63 (14)	55 (14)	813 (13)	
Obese	577 (15)	58 (13)	63 (16)	866 (14)	
Unknown	2,167 (55)	238 (54)	206 (51)	3,693 (58)	
APACHE III Score: score ≥ 35	2,017 (51)	212 (49)	190 (47)	3,123 (49)	0.209
Charlson Comorbidity Index: median (range[e]) score	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)	0.003
Diabetes	1,732 (44)	175 (40)	154 (38)	2,592 (41)	0.009
Renal disease	845 (21)	97 (22)	79 (20)	1,254 (20)	0.164
Chronic heart failure	790 (20)	77 (18)	65 (16)	1,173 (18)	0.106
Other infections					
Pneumonia	723 (18)	60 (14)	60 (15)	1,022 (16)	0.006
Osteomyelitis	560 (14)	30 (7)	52 (13)	562 (9)	< 0.001
Endocarditis	215 (5)	7 (2)	20 (5)	269 (4)	< 0.001
Dialysis	49 (1)	9 (2)	8 (2)	76 (1)	0.241
Previous positive MRSA culture	314 (8)	54 (12)	40 (10)	636 (10)	< 0.001
Secondary MSSA infection	59 (1)	8 (2)	6 (2)	126 (2)	0.317
Positive culture for an organism other than *Staphylococcus aureus* during admission	2,341 (59)	210 (48)	237 (659)	3,355 (53)	< 0.001
Positive MRSA nasal culture	51 (1)	2 (<1)	8 (2)	69 (1)	0.158
Hospital-onset infection[f]	1,123 (28)	123 (28)	117 (29)	1,940 (30)	0.128
Penicillin allergy	329 (8)	113 (26)	46 (11)	602 (9)	< 0.001

Table 4.10 Continued

Length of stay in the hospital: median (range[e]) days[g]	15 (9-34)	10 (7-14)	16 (11-30)	8 (4-20)	< 0.001
30-day mortality[h]	554 (14)	56 (13)	69 (17)	1,346 (21)	< 0.001

[a] Definitive treatment is defined as starting or remaining on an antimicrobial between ≥ 4 days after the day the first blood culture that grew MSSA was collected until 14 days after the day the first blood culture that grew MSSA was collected.

[b] The numbers in parentheses are percentages unless otherwise specified.

[c] Patients received definitive treatment with vancomycin and a β-lactam.

[d] Patients received definitive treatment that did not include vancomycin or a β-lactam.

[e] Interquartile range.

[f] Positive MSSA culture occurred > 2 days after admission.

[g] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

[h] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained.

Table 4.11: Characteristics of patients who received definitive treatment with a β-lactam or vancomycin for their MSSA bacteremia who died compared with patients who survived[a]

Characteristic	Patients who Died N=610[b, c]	Patients who Survived N=3,791	P-value
Gender	602 (99)	3,699 (98)	0.086
Age : ≥ 63 years	410 (67)	1,798 (47)	< 0.001
Body Mass Index			< 0.001
Underweight	33 (5)	93 (2)	
Normal	90 (15)	505 (13)	
Overweight	98 (16)	542 (14)	
Obese	57 (9)	578 (15)	
Unknown	332 (54)	2,073 (55)	
APACHE III Score: score ≥ 35	429 (70)	1,800 (47)	< 0.001
Charlson Comorbidity Index: median (range[d]) score	3 (1-5)	2 (1-4)	< 0.001
Diabetes	192 (31)	1,715 (45)	< 0.001
Renal disease	125 (20)	817 (22)	0.554
Chronic heart failure	162 (27)	705 (19)	< 0.001
Other infections			
Pneumonia	168 (28)	615 (16)	< 0.001
Osteomyelitis	33 (5)	557 (15)	< 0.001
Endocarditis	45 (7)	177 (5)	0.005
Dialysis	4 (1)	54 (1)	0.122
Previous positive MRSA culture	39 (6)	329 (9)	0.059
Secondary MSSA infection	13 (2)	54 (1)	0.186
Positive culture for an organism other than *Staphylococcus aureus* during admission	407 (67)	2,144 (57)	< 0.001
Positive MRSA nasal culture	11 (2)	42 (1)	0.144
Hospital-onset infection[e]	238 (39)	1,008 (27)	< 0.001
Penicillin allergy	34 (6)	408 (11)	< 0.001
Length of stay in the hospital: median (range[d]) days[f]	12 (9-18)	14 (9-36)	< 0.001

[a] Definitive treatment is defined as starting or remaining on an antimicrobial between ≥ 4 days after the day the first blood culture that grew MSSA was collected until 14 days after the day the first blood culture that grew MSSA was collected.

[b] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained

[c] The numbers in parentheses are percentages unless otherwise specified.

[d] Interquartile range.

[e] Positive MSSA culture occurred > 2 days after admission.

[f] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

Table 4.12: Survival regression models comparing patients with MSSA bacteremia who received definitive treatment with a β-lactam versus patients who received vancomycin (N=4,401)[a]

Model	Variable	Hazard Ratio (95% CI)	P-value
Unadjusted	β-lactam vs. vancomycin	0.67 (0.51-0.88)	0.004
Adjusted[b]	β-lactam vs. vancomycin	0.66 (0.50-0.87)	0.003
	APACHE III Score[c]	2.19 (1.80-2.66)	< 0.001
	Charlson Comorbidity Index	1.04 (1.00-1.07)	0.026
	Age[d]	1.64 (1.38-1.95)	< 0.001
	Diabetes	0.50 (0.42-0.60)	< 0.001
	Heart disease	1.25 (1.04-1.50)	0.020
	Osteomyelitis	0.38 (0.27-0.54)	< 0.001
	Penicillin allergy	0.54 (0.38-0.76)	< 0.001

[a] Definitive treatment is defined as starting or remaining on an antimicrobial between ≥ 4 days after the day the first blood culture that grew MSSA was collected until 14 days after the day the first blood culture that grew MSSA was collected.

[b] APACHE III Score and Charlson Comorbidity Index were forced in the model.

[c] Acute Physiology and Chronic Health Evaluation (APACHE) III score; reference is < 35 points.

[d] Reference is < 63 years old.

Table 4.13: Characteristics of patients with MSSA bacteremia who received empiric treatment with either a first generation cephalosporin or antistaphylococcal penicillin compared with patients who received vancomycin[a]

Characteristic	Received First Generation Cephalosporin or Antistaphylococcal Penicillin N=682[b]	Received Vancomycin N=1,912	P-value
Gender	673 (99)	1,863 (97)	0.059
Age: ≥ 63 years	316 (46)	969 (51)	0.051
Body Mass Index			
Underweight	20 (3)	51 (3)	
Normal	98 (14)	263 (14)	
Overweight	80 (12)	278 (15)	
Obese	100 (15)	255 (13)	
Unknown	384 (56)	1,065 (56)	
APACHE III Score: score ≥ 35	309 (45)	913 (48)	0.273
Charlson Comorbidity Index: median (range[c]) score	2 (1-4)	2 (1-4)	0.016
Diabetes	291 (43)	767 (40)	0.244
Renal disease	127 (19)	442 (23)	0.015
Chronic heart failure	124 (18)	359 (19)	0.732
Other infections			
Pneumonia	83 (12)	251 (13)	0.522
Osteomyelitis	86 (13)	163 (9)	0.002
Endocarditis	42 (6)	75 (4)	0.016
Dialysis	10 (1)	4 (3)	0.713
Previous positive MRSA culture	47(7)	195 (10)	0.011
Secondary MSSA infection	27(4)	25 (1)	< 0.001
Positive culture for an organism other than *Staphylococcus aureus* during admission	298 (44)	999 (52)	< 0.001
Positive MRSA nasal culture	4 (1)	25 (1)	0.124
Hospital-onset infection[d]	222 (33)	594 (31)	0.474
Penicillin allergy	42 (6)	1,343 (18)	< 0.001
Other empirical antimicrobials			
Clindamycin	33 (5)	160 (8)	0.003
Aminoglycosides	68 (10)	255 (13)	0.022
Quinolones	127 (19)	720 (38)	< 0.001
Macrolides	33 (5)	64 (3)	0.078
Trim/Sulfa[e]	25 (4)	74 (4)	0.811
Linezolid	23 (3)	14 (1)	< 0.001
Length of stay in the hospital: median (range[c]) days[f]	11 (6-29)	10 (5-22)	0.368
30-day mortality[g]	81 (12)	288 (15)	0.041

[a] Empiric treatment is defined as starting an antimicrobial between two days before the day of the first blood culture that grew MSSA was collected until four days after the first blood culture that grew MSSA was collected.

Table 4.13 Continued

[b] The numbers in parentheses are percentages unless otherwise specified.

[c] Interquartile range.

[d] Positive MSSA culture occurred > 2 days after admission.

[e] Trimethoprim/sulfamethoxazole.

[f] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

[g] Defined as death occurring within the 30 days immediately after the day when the first culture that grew MSSA was obtained.

Table 4.14: Characteristics of patients who received empiric treatment with a first generation cephalosporin, antistaphylococcal penicillin or vancomycin for MSSA bacteremia who died compared with patients who survived[a]

Characteristic	Patients who Died[b, c] N=369	Patients who Survived N=2,225	P-value
Gender	2,173 (98)	363 (98)	0.392
Age: ≥ 63 years	256 (69)	1,029 (46)	< 0.001
Body Mass Index			0.013
Underweight	15 (4)	56 (3)	
Normal	51 (14)	310 (14)	
Overweight	56 (15)		
Obese	31 (8)	324 (15)	
Unknown	216 (59)	1,233 (55)	
APACHE III Score: score ≥ 35	253 (69)	969 (44)	< 0.001
Charlson Comorbidity Index: median (range[d]) score	3 (1-5)	2 (1-3)	< 0.001
Diabetes	938 (42)	120 (33)	< 0.001
Renal disease	73 (20)	496 (22)	0.281
Chronic heart failure	108 (29)	375 (17)	< 0.001
Other infections			
Pneumonia	77 (21)	257 (12)	< 0.001
Osteomyelitis	13 (4)	236 (11)	< 0.001
Endocarditis	94 (4)	23 (6)	0.085
Dialysis	3 (1)	39 (2)	0.185
Previous positive MRSA culture	24 (7)	218 (10)	0.044
Secondary MSSA infection	10 (3)	42 (2)	0.297
Positive culture for an organism other than *Staphylococcus aureus* during admission	208 (56)	1,089 (49)	0.008
Positive MRSA nasal culture	5 (1)	24 (1)	0.640
Hospital-onset infection[e]	157 (43)	659 (30)	< 0.001
Penicillin allergy	53 (14)	332 (15)	0.780
Other empirical antimicrobials			
Clindamycin	24 (7)	169 (8)	0.459
Aminoglycosides	44 (12)	279 (13)	0.740
Quinolones	159 (43)	688 (31)	< 0.001
Macrolides	14 (4)	83 (4)	0.952
Trim/Sulfa[f]	12 (3)	87 (4)	0.541
Linezolid	6 (2)	31 (1)	0.727
Length of stay in the hospital: median (range[d]) days[g]	8 (3-14)	11 (6-27)	< 0.001

[a] Empiric treatment is defined as starting an antimicrobial between two days before the date of the first positive MSSA blood culture until four days after the first positive blood culture.

[b] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained.

Table 4.14 Continued

[c] The numbers in parentheses are percentages unless otherwise specified.

[d] Interquartile range.

[e] Positive MSSA culture occurred > 2 days after admission.

[f] Trimethoprim/sulfamethoxazole.

[g] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

Table 4.15: Survival regression models comparing patients with MSSA bacteremia who received empiric treatment with either a first generation cephalosporin or antistaphylococcal penicillin versus patients who received vancomycin (N=2,594)[a]

Model	Variable	Hazard Ratio (95% CI)	P-value
Unadjusted	β-lactam vs. vancomycin	0.74 (0.58-0.95)	0.018
Adjusted[b]	β-lactam vs. vancomycin	0.82 (0.64-1.05)	0.121
	APACHE III Score[c]	2.33 (1.81-2.99)	< 0.001
	Charlson Comorbidity Index	1.04 (1.00-1.08)	0.077
	Age[d]	1.81 (1.43-2.27)	< 0.001
	Diabetes	0.53 (0.42-0.67)	< 0.001
	Heart disease	1.39 (1.10-1.75)	0.005
	Osteomyelitis	0.33 (0.19-0.58)	< 0.001

[a] Empiric treatment is defined as starting an antimicrobial between two days before the date of the first positive blood culture until four days after the first positive blood culture.

[b] APACHE III Score and Charlson Comorbidity Index were forced in the model.

[c] Reference is < 35 points.

[d] Reference is < 63 years old.

Table 4.16: Survival regression models comparing patients with MSSA bacteremia who received empiric treatment with either a first generation cephalosporin or antistaphylococcal penicillin versus patients who received vancomycin stratified by age, APACHE III score, renal disease, and empiric treatment with a quinolone (N=2,594)[a]

	Stratified Variable							
	Age[b]		**APACHE Score[b]**		**Renal Disease[c]**		**Empiric Quinolone[c]**	
	≥ 63 years	**< 63 year**	**≥ 35 points**	**< 35 points**	**Yes**	**No**	**Yes**	**No**
Variables in Model[d]	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
β-lactam vs. vancomycin	0.56 (0.40-0.79)	1.52 (1.03-2.23)	0.646 (0.47-1.08)	1.269 (0.86-1.88)	0.44 (0.22-0.86)	0.91 (0.70-1.19)	0.70 (0.43-1.14)	0.94 (0.70-1.26)
APACHE III Score[e]	2.11 (1.56-2.87)	2.73 (1.76-4.23)	_____	_____	2.47 (1.24-4.92)	2.31 (1.76-3.03)	2.19 (1.49-3.22)	2.31 (1.66-3.23)
Charlson Comorbidity Index	1.04 (0.99-1.09)	1.037 (0.97-1.11)	1.03 (0.99-1.08)	1.05 (0.93-1.19)	0.99 (0.89-1.11)	1.06 (1.02-1.11)	1.046 (0.99-1.11)	1.03 (0.98-1.09)
Age[f]	_____	_____	1.68 (1.26-2.24)	2.030 (1.39-2.97)	2.36 (1.30-4.27)	1.75 (1.36-2.25)	1.79 (1.25-2.58)	1.77 (1.31-2.39)
Diabetes	0.56 (0.42-0.74)	0.51 (0.33-0.77)	0.53 (0.41-0.69)	0.57 (0.33-1.00)	0.79 (0.49-1.28)	0.51 (0.39-0.67)	0.51 (0.36-0.73)	0.55 (0.41-0.75)

Table 4.16 Continued

Heart disease	1.36 (1.05-1.76)	1.49 (0.90-2.45)	1.30 (0.99-1.72)	1.65 (1.07-2.56)	1.62 (1.00-2.61)	1.46 (1.11-1.92)	1.16 (0.81-1.68)	1.60 (1.18-2.15)
Osteomyelitis	0.49 (0.26-0.93)	0.17 (0.05-0.52)	0.32 (0.16-0.64)	0.363 (0.15-0.90)	0.08 (0.01—0.61)	0.43 (0.24-0.77)	0.46 (0.20-1.05)	0.27 (0.13-0.58)

[a] Empiric treatment is defined as starting an antimicrobial between two days before the day the first blood culture that grew MSSA was collected until four days after the day the first blood culture that grew MSSA was collected.

[b] APACHE III score and age were effect modifiers.

[c] Renal disease and receiving empiric quinolone violated the proportional hazard assumption.

[d] APACHE III Score and Charlson Comorbidity Index were forced in the model.

[e] Reference is < 35 points.

[f] Reference is < 63 years old.

Table 4.17: Characteristics of patients with MSSA bacteremia who received definitive treatment with a either a first generation cephalosporin or antistaphylococcal penicillin compared with patients who received vancomycin[a]

Characteristic	Received First Generation Cephalosporin or Antistaphylococcal Penicillin N=2,926 [b]	Received Vancomycin N=437	P-value
Gender	2,862 (98)	420 (96)	0.030
Age: ≥ 63 years	1,445 (49)	213 (49)	0.802
Body Mass Index			0.783
Underweight	75 (3)	14 (3)	
Normal	397 (14)	64 (15)	
Overweight	424 (15)	63 (14)	
Obese	441 (15)	58 (13)	
Unknown	1,589 (54)	238 (54)	
APACHE III Score: score ≥ 35	1,474 (50)	212 (49)	0.467
Charlson Comorbidity Index: median (range[c]) score	2 (1-4)	2 (1-4)	0.0978
Diabetes	1,260 (43)	175 (40)	0.234
Renal disease	654 (22)	97 (22)	0.942
Chronic heart failure	573 (20)	77 (18)	0.332
Other infections			
Pneumonia	480 (16)	60 (14)	0.155
Osteomyelitis	426 (15)	30 (7)	< 0.001
Endocarditis	177 (6)	7 (2)	< 0.001
Dialysis	44 (2)	9 (2)	0.384
Previous positive MRSA culture	196 (7)	54 (12)	< 0.001
Secondary MSSA infecion	38 (1)	8 (2)	0.372
Positive culture for an organism other than *Staphylococcus aureus* during admission	1,620 (55)	210 (48)	0.004
Positive MRSA nasal culture	34 (1)	2 (<1)	0.182
Hospital-onset infection[d]	775 (26)	123 (28)	0.464
Penicillin allergy	247 (8)	113 (26)	< 0.001
Length of stay in the hospital: median (range[c]) days[e]	15 (9-33)	10 (7-14)	< 0.001
30-day mortality[f]	372 (13)	56 (13)	0.953

[a] Definitive treatment is defined as starting or still taking an antimicrobial between ≥ 4 days after the date of the first positive MSSA blood culture until 14 days after the first positive blood culture.

[b] The numbers in parentheses are percentages unless otherwise specified.

[c] Interquartile range.

[d] Positive MSSA culture occurred > 2 days after admission.

Table 4.17 Continued

[e] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

[f] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained

Table 4.18: Characteristics of patients who received definitive treatment with a first generation cephalosporin, antistaphylococcal penicillin, or vancomycin for their MSSA bacteremia who died compared with patients who survived[a]

Characteristic	Patients who Died[b, c] N=428	Patients who Survived N=2,935	P-value
Gender	423 (99)	2,859 (97)	0.073
Age: ≥ 63 years	288 (67)	1,370 (47)	<0.001
Body Mass Index			0.001
Underweight	20 (5)	69 (2)	
Normal	60 (14)	401 (14)	
Overweight	69 (16)	418 (14)	
Obese	41 (10)	458 (16)	
Unknown	238 (56)	1,589 (54)	
APACHE III Score: score ≥ 35	299 (70)	1,387 (47)	<0.001
Charlson Comorbidity Index: median (range[d]) score	3 (1-5)	2 (1-4)	<0.001
Diabetes	135 (32)	1,300 (44)	<0.001
Renal disease	92 (22)	659 (22)	0.657
Chronic heart failure	121 (28)	529 (18)	<0.001
Other infections			
Pneumonia	116 (27)	424 (14)	<0.001
Osteomyelitis	25 (6)	431 (15)	<0.001
Endocarditis	32 (7)	152 (5)	0.051
Dialysis	4 (1)	49 (2)	0.254
Previous positive MRSA culture	25 (6)	225 (8)	0.179
Secondary MSSA infection	10 (2)	36 (1)	0.065
Positive culture for an organism other than *Staphylococcus aureus* during admission	277 (65)	1,553 (53)	<0.001
Positive MRSA nasal culture	4 (1)	32 (1)	0.770
Hospital-onset infection[e]	163 (38)	735 (25)	<0.001
Penicillin allergy	30 (7)	330 (11)	0.008
Length of stay in the hospital: median (range[d]) days[f]	12 (8-17)	14 (9-34)	<0.001

[a] Definitive treatment is defined as starting or still taking an antimicrobial between ≥ 4 days after the day the first blood culture that grew MSSA was collected until 14 days after the day the first blood culture that grew MSSA was collected.

[b] Defined as death occurring within the 30 days immediately after the date when the first culture that grew MSSA was obtained

[c] The numbers in parentheses are percentages unless otherwise specified.

[d] Interquartile range.

[e] Positive MSSA culture occurred > 2 days after admission.

[f] Defined as the day the first blood culture that grew MSSA was collected until the patient was either discharged from the hospital or died.

Table 4.19: Survival regression models comparing patients with MSSA bacteremia who received definitive treatment with either a first generation cephalosporin or an antistaphylococcal penicillin versus patients who received vancomycin (N=3,363)[a]

Model	Variable	Hazard Ratio (95% CI)	P-value
Unadjusted	β-lactam vs. vancomycin	0.62 (0.47-0.83)	0.001
Adjusted[b]	β-lactam vs. vancomycin	0.62 (0.47-0.83)	0.001
	APACHE III Score[c]	2.05 (1.62-2.58)	< 0.001
	Charlson Comorbidity Index	1.05 (1.01-1.09)	0.006
	Age[d]	1.66 (1.35-2.05)	< 0.001
	Diabetes	0.51 (0.41-0.63)	< 0.001
	Heart disease	1.36 (1.09-1.69)	0.006
	Osteomyelitis	0.41 (0.28-0.62)	< 0.001
	Penicillin allergy	0.63 (0.43-0.92)	0.016

[a] Definitive treatment is defined as starting or still receiving an antimicrobial between ≥ 4 days after the day the first blood culture that grew MSSA was collected until 14 days after the first day the first blood culture that grew MSSA was collected.

[b] APACHE III Score and Charlson Comorbidity Index were forced in the model.

[c] Reference is < 35 points.

[d] Reference is < 63 years old.

CHAPTER 5

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) PREVENTION PRACTICES IN HOSPITALS THROUGHOUT A RURAL STATE

Abstract

Background: The Institute for Healthcare Improvement (IHI) created an evidence-based bundle to help reduce methicillin-resistant *Staphylococcus aureus* (MRSA) healthcare-associated infections. This aim of this study is to identify which components of the IHI MRSA bundle rural hospitals have implemented and to identify barriers that hindered implementation of bundle components.

Methods: Four surveys about the IHI MRSA bundle were administered at the Iowa Statewide Infection Prevention Seminar between 2007 and 2011. Surveys were mailed to infection preventionists (IPs) who did not attend the meetings.

Results: During the study period, the percent of IPs reporting that their hospital implemented a hand hygiene program (range: 87%-94%) and used contact precautions for patients infected (range: 97%-100%) or colonized (range: 77%-92%) with MRSA did not change significantly. The number of hospitals that monitored the effectiveness of environmental cleaning significantly increased over the study period (range by year: 23%-71%; $P < 0.01$). In hospitals caring for patients with central lines (CL; N = 47-69), the CL bundle component performed by the least number of hospitals was assessing each day if the CL was necessary (range by year: 22%-26%). The majority of IPs at hospitals caring for ventilated patients (N = 25-34) reported that staff performed all components of the ventilator bundle (range by year: 59%-94%). IPs perceived lack of support to be a major barrier to implementing MRSA bundle components.

Conclusions: The majority of IPs reported that their hospitals had implemented most components of the MRSA bundle. Support within the healthcare system is essential for implementing each component of an evidence-based bundle.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most prevalent antimicrobial-resistant organism causing healthcare-associated infections in the United States (48, 49). MRSA transmission is common in hospitals, where it is spread from patient to patient on healthcare worker's hands, by contaminated environments, or directly from patient to patient. Additionally, hospitalized patients are vulnerable to MRSA infections because they often have indwelling devices, are immunosuppressed, or have had surgical procedures. Treatment options are limited for patients with MRSA infections. In addition, outcomes of MRSA infections may be worse than for MSSA infections and the costs of treating MRSA infections may be higher than those for MSSA infections (50, 51).

Several organizations have developed evidence-based guidelines to help healthcare providers reduce MRSA healthcare-associated infections in acute care hospitals and other healthcare facilities (20, 56, 57). The Institute for Healthcare Improvement's (IHI) 5 Million Lives Campaign included a five-component evidence-based bundle to help reduce MRSA transmission and infections (189). Numerous hospitals have implemented some or all of the bundle components. However, investigators have examined bundle implementation primarily at single centers in large urban areas and/or have focused on a few of the bundle components (101-104). The current study assessed implementation of the bundle by multiple hospitals located throughout a single rural U.S. state. Additionally, this study assessed infection preventionists' (IPs) self-reports of perceived barriers to implementing the IHI MRSA bundle and factors that facilitated implementation.

Methods

Surveys

We conducted statewide longitudinal cross-sectional surveys of IPs working at acute care hospitals in Iowa. IPs completed the surveys in 2007, 2009, 2010, and 2011.

Surveys were given to IPs during the annual Iowa Statewide Infection Prevention Seminar and surveys were mailed to IPs who did not attend the seminar. A list of IPs attending the conference and a list of hospitals in Iowa were used to determine which IPs would receive surveys by mail.

The questions in the survey were primarily descriptive and most addressed the five components of the IHI MRSA bundle: 1) hand hygiene; 2) decontamination of the environment and equipment; 3) active surveillance for MRSA; 4) contact precautions for infected and colonized patients; 5) the central line (CL) and ventilator bundles (Table 5.1) (189). The CL bundle included five interventions: 1) hand hygiene before inserting, using, or caring for a CL; 2) sterile barrier precautions when inserting a CL; 3) chlorhexidine for skin antisepsis when inserting a CL and for site care; 4) catheters inserted in the optimal vein; 5) daily assessment of the catheter's necessity and removing unnecessary catheters (189). The ventilator bundle included five interventions: 1) elevate the head of the patient's bed to 30-45 degrees; 2) use "sedation vacations" or reduce use of sedatives daily; 3) review the patient daily for readiness to extubate or wean; 4) prescribe peptic ulcer prophylaxis; 5) prescribe deep venous thrombosis prophylaxis (189). Additionally, the survey included open-ended questions regarding the top three facilitators and barriers that affected implementation of bundle components. Two independent reviewers categorized the facilitators and barriers, and a third reviewer adjudicated disagreements. (Appendix B: Survey from 2011)

Analysis

Data from the surveys were entered into an Excel spreadsheet and analyzed using SAS software (SAS Institute, Cary, NC) version 9.3. Frequency distributions were calculated and chi-square and Fisher's exact tests were used to examine the difference between the numbers of hospitals performing the bundle component throughout each year of the study period. Statistical significance was defined as $P < 0.05$. The Cochran-

Armitage trend test was performed to analyze the change over time on statistically significant variables identified by the chi-square and Fisher's exact tests.

Results

The percent of hospitals participating in the survey increased over the study period (2007: 55%; 2009: 63%; 2010: 72%; 2011: 73%), but hospital characteristics did not vary significantly (Table 5.1). Most of the hospitals had ≥ 25 acute care beds (range by year: 48%-63%) and 55%-71% were located in communities with populations with ≤ 10,000 residents. Over half of the hospitals had an on-site laboratory (range by year: 64%-71%) and part-time IPs (range by year: 61%-66%).

Many of the responding hospitals reported that their hospital implemented the IHI MRSA bundle components, but fewer reported that the hospital's staff monitored adherence to bundle components and reported the results back to staff (Table 5.2). The majority of the respondents indicated that their hospitals had a hand hygiene program (range by year: 87%-94%) and placed patients infected or colonized with MRSA in contact precautions (range by year: 77%-100%). The number of respondents reporting that their hospitals monitored environmental cleaning (range by year: 23%-71%) and the number of hospitals reporting that they observed hand hygiene adherence and reported the results to staff increased during the study period (range by year: 68%-89%). The percent of respondents reporting that their hospital performed all of the MRSA bundle components, except for the device related components, increased significantly from 2% in 2007 to 45% in 2010 ($P < 0.01$). Subsequently, the rate decreased slightly to 39% in 2011.

Active surveillance methods differed among the hospitals, and some hospitals performed active surveillance even though their hospital did not have a laboratory on site (Table 5.3). Most respondents reported that their facilities assessed patients that had a prior history of MRSA infection or colonization (range by year: 57%-72%). The percent of respondents reporting that their hospitals screened specific patient populations (range

by year: 60%-63%) or patients admitted to a specific unit (range by year: 21%-22%) remained stable from 2009-2011. Most respondents reported collecting specimens on admission from either the nares only (range by year: 24%-36%); or the nares, sites of previous infections, and wounds (range by year: 32%-43%). Less than 30% of the respondents reported that their hospital did not perform active surveillance testing (2009: 24%; 2010: 21%; 2011: 26%), and the most common reasons for not doing surveillance were "lack of support from their physicians" (range by year: 22%-48%), and active surveillance testing "was not considered an appropriate control strategy for their facility" (range by year: 26%-50%).

Over 60% (range by year: 63%-78%) of IPs reported that their staff inserted CLs, and over 70% of these respondents reported that their staff used maximum sterile barrier precautions (range by year: 86%-96%), used chlorhexidine to prepare the skin (range by year: 74%-99%), and/or preferentially inserted catheters into the subclavian vein (range by year: 73%-78%; Table 5.4). From 2007-2011, the number of respondents reporting that their hospitals used chlorhexidine for skin antisepsis before inserting the catheter increased significantly from 74% in 2007 to 99% in 2011 ($P < 0.01$). Less than 30% of the respondents indicated that their staff determined if the catheter was necessary each day and removed unnecessary catheters (range by year: 22%-26%). From 2007-2011, the percent of respondents reporting that their hospital observed adherence and provided feedback to staff regarding use of maximum sterile barrier precautions (range by year: 44%-58%), use of chlorhexidine (range by year: 46%-59%), and the vein used for insertion (range by year: 31%-52%) increased, but the differences did not reach statistical significance.

Less than half of the respondents reported that their staff placed patients on ventilators (range by year: 33%-45%; Table 5.5). Among respondents that placed patients on ventilators, the percent of respondents reporting that their hospital staff elevated the head of the patient's bed (range by year: 85%-94%), used "sedation vacations" or

reduced sedatives (range by year: 59%-82%), reviewed the patient daily to assess readiness to be extubated (range by year:72%-91%), prescribed peptic ulcer prophylaxis (range by year: 62%-88%), and prescribed deep venous thrombosis prophylaxis (range by year: 62%-91%) increased from 2007-2011, but the changes did not reach statistical significance. Additionally, the percent of hospitals that observed adherence and reported results to staff for elevating the head of the patient's bed (range by year: 64%-77%), using "sedation vacations" or reducing sedatives (range by year: 50%-81%), and reviewing the patient daily to assess readiness to be extubated (range by year: 46%-80%) increased but the changes did not reach statistical significance.

Relationships were examined to identify differences in implementing IHI MRSA bundle components across hospital characteristics (Table 5.6). In general, there were not any hospital characteristics that were associated with a particular bundle component throughout the entire study period. Larger hospitals or the hospitals employing more IPs were more likely to implement the ventilator bundles ($P < 0.001$ for each year). Among the hospitals that placed patients on ventilators, the test for trend indicated that hospitals with a larger bed size were more likely to elevate the head of the patient's bed (Year: 2007; $P = 0.005$), use "sedation vacations" (Year: 2009, 2010; $P = 0.023$, 0.011), review the patient for extubation (Year:2010; $P = 0.044$), prescribe peptic ulcer prophylaxis (Year: 2010; $P < 0.001$), or prescribe deep venous thrombosis prophylaxis (Year: 2007; $P = 0.005$) for at least one year within the study period. Hospitals employing more IPs were less likely to observe adherence to prescribing deep vein thrombosis prophylaxis (Year: 2010; $P = 0.041$). Having a laboratory at the hospital was associated with implementing active surveillance culturing (Year: 2011; $P = 0.019$).

One hundred thirty IPs provided 330 responses in 2010 and 2011 describing factors that were perceived to facilitate implementation of the IHI MRSA bundle components at their hospitals. The 330 responses were placed into eleven categories (Table 5.7). The three most common responses pertained to having support from within

the hospital (34%), performing a specific intervention (19%), and having the capability to identify patients colonized with MRSA (11%). One hundred eleven responses pertained to having support from infection control personnel (28%), administrators (26%), healthcare workers (23%), physicians (12%), laboratory workers (5%), environmental services personnel (3%), and network/regional systems (2%). Sixty-four responses mentioned a specific intervention--hand hygiene (22%) and contact precautions (30%)--that helped staff implement the bundle. Thirty-five responses related to having resources that allowed the IP to identify patients colonized with MRSA, which included identifying patients through laboratory methods such as cultures or PCR and being able to flag the medical records of patients colonized or previously infected with MRSA.

One hundred thirty-eight IPs provided 318 responses in 2010 and 2011 regarding factors that they perceived were barriers to implementation of IHI MRSA bundle components. The 318 responses were separated into eleven categories (Table 5.8). The three most common barriers were lack of support (27%), inadequate funding (11%), and lack of time (10%). Seventy-two responses pertained to lack of support by physicians (53%), healthcare workers (38%), or administrators (10%). Poor adherence to bundle components is actually an outcome of poor bundle implementation. However, 20% of the comments about barriers addressed poor adherence among healthcare workers. Sixty-three responses described poor adherence by specific groups of people, poor adherence with specific interventions, or both. Healthcare workers, physicians, and family members were the primary groups of people that did not adhere to recommended practices. The IPs' comments identified implementing contact precautions, doing hand hygiene, and using personnel protective equipment as practices for which adherence was less than optimal.

Of the respondents, 56% (49/88) reported that their rates of hospital-associated MRSA infections declined from 2008 to 2011. In 2011, the survey asked whether hospital-associated infection rates had changed over time. About one quarter to one half

of respondents reported that hospital-associated infection rates decreased: overall hospital-associated infections (45%), catheter-associated bloodstream infections (38%), ventilator-associated pneumonias (18%), surgical site infections (32%), catheter-associated urinary tract infections (32%), *Clostridium difficile* infections (25%), and vancomycin-resistant *Enterococcus* infections (28%).

Discussion

Many of the hospitals participating in our study had < 25 acute care beds and were located in communities with populations with ≤ 10,000 residents. This finding is consistent with the size distribution of hospitals in Iowa and the distribution of hospitals by the Medicare classification. Of the acute care hospitals in Iowa (N = 119 in 2007, N = 120 in 2009-2011), 82 (68%-69%) are Critical Access Hospitals (≤ 25 beds), and 77% of Iowa hospitals are classified by Medicare as Rural (not in a Metropolitan Statistical Area) (190, 191).

The majority of the participating hospitals implemented most of the IHI MRSA bundle components throughout the study period. Other surveys have examined some of these components as well. A survey which included 102 acute care hospitals in 27 states, found that 92% of the facilities had a contact precautions protocol for patients infected or colonized with MRSA (101). Another survey study reported high compliance rates (median ≥80%) for performing hand hygiene practices, using an antimicrobial CL dressing, or placing patients who had MRSA on contact precautions in many of the 99 adult ICUs (bedsize: 50 to >500) (104).

Unlike other bundle components, use of chlorhexidine for skin antisepsis before CL insertion and monitoring environmental cleaning increased significantly from 2007 to 2011. Use of chlorhexidine may have increased given the recommendation in the IHI CL bundle. Monitoring environmental cleaning increased because a grant from the Centers for Disease Control and Prevention, which funded the current study, also funded a study that allowed IPs at numerous hospitals to use a florescent marker and an ultraviolet light

when assessing environmental cleaning (192, 193). Hospitals participating in the florescent marker study likely accounted for most of the increase that we documented in this survey. The percent of hospitals that monitored environmental cleaning decreased somewhat from 2010 to 2011, probably because the environmental monitoring study was completed and the hospitals could no longer acquire the florescent marker free of charge.

The risk of hospital-acquired infections increases the longer a CL is in place and other investigators have reported that staff leave CLs in patients when they are not needed (194, 195). For example, Tejedor et al. found that 63% (56/89) of the patients in their study had an unnecessary CL present for at least one day (195). Indeed, we found that the bundle component performed by the fewest hospitals in our study was determining daily if a CL is necessary. This bundle component may be difficult to implement because staff worry that if they remove a CL they will not have vascular access if the patient's condition worsens. This component is also difficult to implement because it requires physicians to think about a patient's CL every day. Tools such as rounding checklists could help physicians address this issue daily.

Similar to other investigators, we found that support within the hospital, from administrators, physicians, or other healthcare workers, was the facilitating factor IPs mentioned most commonly (196-198). Conversely, IPs most commonly reported lack of support as the major barrier to implementation. We did not ask about specific factors that increased support within hospitals for bundle implementation. However, we wonder if campaigns such as the IHI's 5 Million Lives Campaign, which the Iowa Healthcare Collaborative supported actively, and new guidelines or regulations may have played an important role (199).

The IPs reported that healthcare workers' lack of adherence was a major barrier to implementing MRSA control measures. However, lack of adherence is not a barrier to implementation but an outcome of poor implementation. Indeed, poor adherence may

indicate that the organization has not established a culture of safety, in which adherence is expected.

Other investigators have reported low adherence to infection control practices (200). Zoabi et al. prospectively monitored healthcare workers caring for patients on contact precautions (200). They found active surveillance culturing was performed on only 32% of eligible patients and the mean rate for adherence to hand hygiene was 59% for nurses and 41% for doctors (200). Some investigators have found that the combination of monitoring adherence and reporting the results back to staff helps healthcare workers improve their performance (196, 197, 201). Jamal et al. reported that healthcare workers on different units began competing with each other when hand hygiene adherence rates were provided to all units (196). Langston et al. reported a significant increase in hand hygiene adherence after contact with objects or surfaces in patients' rooms when peers monitored and fed back adherence rates to staff in the surgical intensive care unit, neurosurgery intensive care unit, and the surgical intermediate care unit (201). A substantial proportion of IPs in our study reported that their hospital implemented a specific bundle component, but did not monitor adherence and report results to staff for that component. This was especially true for the CL bundle components for which the percent of hospitals monitoring adherence and reporting back to staff was usually around 50%. Thus, the poor adherence to the bundle components might have been attributable, in part, to lack of monitoring and feedback, which might have been related to inadequate resources.

Our study had several limitations. First, we did not provide each hospital with a study number so that we could assess change in practice at individual hospitals over time. Second, we did not administer the survey in 2008. Third, the survey did not ask respondents to report their actual hospital-acquired infection rates. Therefore, we could not assess whether implementing more components or specific components of the IHI MRSA bundle reduced rates of MRSA infection most effectively. However, a substantial

proportion of the IPs reported reduced rates of all hospital-associated infections, MRSA hospital-associated infections, or specific hospital-associated infection types. This finding is consistent with data on rates of MRSA hospital-associated infections reported voluntarily to the Iowa Healthcare Collaborative. From 2008 to 2010, the rate of MRSA bloodstream infections decreased from 0.05 to 0.02 infections per 1000 patient days and the rate of MRSA surgical site infections decreased 0.45 to 0.29 infections per 100 procedures (personal written communication from Thomas Evans, MD, January 2012).

Other studies have found decreased hospital-associated infection rates after an MRSA bundle was implemented. In 2007, all acute care Veterans Affairs Medical Centers implemented a bundle that included universal active surveillance testing for MRSA on admission, contact precautions for patients colonized or infected with MRSA, a hand hygiene program, and a change in the institutional culture (102). After bundle implementation, the rate of MRSA hospital-associated infections decreased from 1.64 to 0.62 infections per 1000 patient days in the ICUs and from 0.47 to 0.26 infections per 1000 patient-days in non-ICU units (102). Additionally, the investigators reported that hospital-associated infections caused by organisms such as *C. difficile* (1.44 to 0.56 infections per 1000 patient days) or vancomycin-resistant *Enterococcus* (0.33 to 0.09 infections per 1000 patient days) decreased in non-ICU units (102). Awad et al. also reported that MRSA hospital-acquired infections decreased from 2.0 to 1.0 per 1000 bed-days after they implemented an MRSA bundle including active surveillance for MRSA, contact precautions for patients with positive tests, standardized hand hygiene, and monitoring process and outcome measures (103). In addition, they used positive deviance with staff and leaders to facilitate culture change (103).

The IHI 5 Million Lives Campaign included a five component evidence-based bundle to help reduce MRSA transmission and infections. This study assessed implementation of the bundle components in numerous hospitals throughout a rural state. The majority of hospitals reported that they had implemented most bundle components.

However, fewer hospitals reported that they monitor bundle adherence and report adherence rates to staff. Barriers to implementing bundle components included lack of funding, time, and support by physicians. Support from hospital staff such as infection control personnel, healthcare workers, and physicians was essential to implementing the MRSA bundle components. Therefore, support from hospital and physician leadership may be vital in allowing infection prevention and control programs to effectively implement bundles throughout the hospital. Additionally, infection prevention and control programs need to monitor adherence and communicate results to staff to ensure that staff actually implement bundle components.

Table 5.1: Characteristics of hospitals participating in the survey; 2007, 2009-2011

	Year				
Hospital Characteristic	**2007 N = 65 (%)**	**2009 N = 75 (%)**	**2010 N = 86 (%)**	**2011 N = 88 (%)**	**P-value**
Number of Beds					0.183
< 25	24 (37)	30 (40)	42 (49)	46 (52)	
≥ 25	41 (63)	45 (60)	44 (51)	42 (48)	
Community Size					0.175
≤ 10,000	36 (55)	53 (71)	61 (71)	59 (67)	
> 10,000	29 (45)	29 (29)	25 (29)	29 (33)	
Number of Infection Preventionists					0.960
< 1	43 (66)	48 (64)	54 (63)	54 (61)	
≥ 1	22 (34)	27 (36)	32 (37)	33 (38)	
On Site Laboratory					0.754
Yes	43 (66)	53 (71)	58 (67)	56 (64)	

Table 5.2: Components of the Institute for Healthcare Improvement's MRSA bundle implemented by participating hospitals by survey year

	Year				
Component	**2007 N = 65 (%)**	**2009 N = 75 (%)**	**2010 N = 86 (%)**	**2011 N = 88 (%)**	**P-value**
Teach hand hygiene	59 (91)	65 (87)	80 (93)	83 (94)	0.223
Observe adherence and report results to staff (hand hygiene)[a]	40 (68)	53 (82)	71 (89)	74 (89)	0.003
Monitor environmental cleaning	15 (23)	50 (59)	61 (71)	44 (50)	< 0.001[b]
Obtain cultures[a]	5 (33)	10 (20)	6 (10)	7 (16)	____
Observe Housekeepers[a]	7 (47)	22 (44)	26 (43)	24 (55)	____
Use fluorescent marker to monitor[a]	1 (7)	41 (82)	47 (78)	30 (68)	____
Other methods[a]	2 (13)	1 (2)	3 (5)	3 (7)	____
Perform active surveillance testing	38 (58)	56 (75)	68 (79)	65 (74)	0.100
Place infected patients in contact precautions	63 (97)	75 (100)	84 (98)	88 (100)	0.244
Place colonized patients in contact precautions	50 (77)	66 (88)	74 (86)	81 (92)	0.149
Observe adherence and report results to staff (contact precautions)[a]	28 (56)	48 (73)	50 (68)	56 (69)	0.067

[a] The denominator is the number of hospitals performing the component rather than the number of hospitals responding to the survey for that year.

[b] During the study period numerous hospitals participated in a study that provided a fluorescent marker and an ultraviolet light for monitoring the effectiveness of cleaning. Additionally, in 2009-2011 the respondents provided more than one answer for monitoring methods, whereas, in 2007 the respondents only provided one answer.

Table 5.3: Methods for implementing active surveillance testing by survey year

Method	Year 2007 N = 41 (%)	2009 N = 56 (%)	2010 N = 68 (%)	2011 N = 65 (%)	P-value
Types of Patients[a]					
Patients with a prior history of MRSA	____	32 (57)	49 (72)	42 (65)	0.221
Specific patient populations[b]	____	35 (63)	41 (60)	41 (63)	0.941
Specific units[c]	____	12 (21)	15 (22)	14 (22)	0.996
All patients	____	7 (13)	6 (9)	3 (5)	0.297
PCR test available[a]	____	12 (21)	13 (19)	20 (31)	0.286
When specimens obtained					
Admission only	25 (61)	46 (82)	58 (85)	57 (88)	0.017
Other	14 (34)	10 (17)	10 (15)	8 (12)	____
Body site evaluated					
Nares only	10 (24)	20 (36)	20 (29)	22 (34)	0.618
Nares and sites of previous infection	4 (10)	10 (18)	11 (16)	16 (25)	0.256
Nares, sites of previous infection, and wounds	13 (32)	22 (39)	29 (43)	22 (34)	0.652
Sites of previous infections only	3 (7)	1 (2)	2 (3)	1 (2)	0.426
Wounds only	3 (7)	0 (0)	4 (6)	0 (0)	0.019
Other sites	8 (20)	3 (5)	3 (4)	4 (6)	____

[a] Data were not available for 2007.

[b] This includes transfers from other hospitals or long-term care facilities, patients receiving dialysis, patients undergoing total joint replacements, patients with indwelling devices, prisoners, surgical patients, patients with open wounds, patients who were previously hospitalized, and oncology patients.

[c] This includes adult intensive care units (ICU), neonatal ICU, medical/surgical ICU, pediatrics ICU, and bone marrow transplant units.

Table 5.4: Components of the Institute for Healthcare Improvement's central line (CL) bundle implemented by participating hospitals by survey year

	Year				
Component	**2007 N = 50 (%)**	**2009 N = 47 (%)**	**2010 N = 66 (%)**	**2011 N = 69 (%)**	**P-value**
Sterile barrier precautions when inserting CL	43 (86)	42 (89)	61 (92)	66 (96)	0.442
Observe adherence and report results to staff (barrier precautions)[a]	19 (44)	21 (50)	34 (56)	38 (58)	0.611
Chlorhexidine for skin antisepsis when inserting CL and for site care	37 (74)	42 (89)	61 (92)	68 (99)	< 0.001
Observe adherence and report results to staff (using chlorhexidine)[a]	17 (46)	20 (48)	36 (59)	37 (54)	0.521
Subclavian vein preferred site for catheter insertion	39 (78)	35 (74)	48 (73)	54 (78)	0.705
Observe adherence and report results to staff (subclavian vein)[a]	12 (31)	18 (51)	25 (52)	28 (52)	0.140
Determine each day if catheter is necessary and remove unnecessary catheters	11 (22)	11 (23)	16 (24)	18 (26)	0.951
Observe adherence and report results to staff (catheter removal)[a]	9 (82)	7 (64)	11 (69)	11 (61)	0.286

[a] The denominator is the number of hospitals performing the component during a specific year rather than the number of hospitals responding to the survey that year.

Table 5.5: Components of the Institute for Healthcare Improvement's ventilator bundle implemented by participating hospitals by survey year

	Year				
Component	**2007 N = 29 (%)**	**2009 N = 25 (%)**	**2010 N = 34 (%)**	**2011 N = 33 (%)**	**P-value**
Elevate the head of the patient's bed to 30 – 45 degrees	25 (86)	22 (88)	29 (85)	31 (94)	0.718
Observe adherence and report results to staff (elevating the bed)[a]	16 (64)	17 (77)	18 (62)	24 (77)	0.598
Use "sedation vacations" or reduce use of sedatives daily	17 (59)	17 (68)	24 (71)	27 (82)	0.498
Observe adherence and report results to staff (sedation vacations)[a]	12 (71)	12 (71)	12 (50)	22 (81)	0.130
Review the patient daily for readiness to be extubated or weaned from the ventilator	21 (72)	21 (84)	28 (82)	30 (91)	0.557
Observe adherence and report results to staff (daily readiness to be extubated)[a]	11 (52)	13 (62)	13 (46)	24 (80)	0.080
Prescribe peptic ulcer prophylaxis	18 (62)	18 (72)	23 (68)	29 (88)	0.207
Observe adherence and report results to staff (peptic ulcer prophylaxis)[a]	14 (78)	13 (72)	11 (48)	18 (62)	0.276
Prescribe deep venous thrombosis prophylaxis	18 (62)	18 (72)	27 (79)	30 (91)	0.081
Observe adherence and report results to staff (deep venous prophylaxis)[a]	15 (83)	12 (67)	16 (59)	22 (73)	0.433

Table 5.5 Continued

[a] The denominator is the number of hospitals performing the component during a specific year rather than the number of hospitals responding to the survey for that year.

Table 5.6: Examination between hospital characteristics and performing Institute for Healthcare Improvement's MRSA bundle components per year

			Year[a]			
Hospital Characteristic[b]	**IHI MRSA Bundle Component**	**Trend[b]**	**2007 P-value**	**2009 P-value**	**2010 P-value**	**2011 P-value**
Hospital Bed Size	Place patients on ventilators	Larger hospitals more likely to perform component	< 0.001	< 0.001	< 0.001	< 0.001
Hospital Bed Size	Elevate the head of the patient's bed to 30 – 45 degrees	Larger hospitals more likely to perform component	0.008	NS	NS	NS
Hospital Bed Size	Use "sedation vacations" or reduce use of sedatives daily	Larger hospitals to perform component	NS	0.023	< 0.001	< 0.001
Hospital Bed Size	Review the patient daily for readiness to be extubated or weaned from the ventilator	Larger hospitals more likely to perform component	NS	NS	0.044	NS
Hospital Bed Size	Prescribe peptic ulcer prophylaxis	Larger hospitals more likely to perform component	NS	NS	< 0.001	NS
Hospital Bed Size	Prescribe deep venous thrombosis prophylaxis	Larger hospitals more likely to perform component	NS	NS	0.042	NS
Hospital Bed Size	Observe adherence and report results to staff for deep venous prophylaxis	No Significant Trend	NS	NS	0.041	NS
Hospital Bed Size	Place central lines (CL)	Larger hospitals more likely to perform component	NS	0.011	NS	NS

Table 5.6 Continued

Hospital Bed Size	Sterile barrier precaution when inserting CL	No Significant Trend	NS	NS	NS	0.025
Hospital Bed Size	Observe adherence and report results to staff for sterile barrier precautions	Larger hospitals more likely to perform component	NS	NS	0.032	NS
Hospital Bed Size	Chlorhexidine for skin antisepsis when inserting CL and for site care	No Significant Trend	NS	NS	NS	0.025
Hospital Bed Size	Determine each day if catheter is necessary and remove unnecessary catheters	No Significant Trend	NS	NS	NS	0.016
Number of IPs	Observe adherence and report results to staff for hand hygiene	No Significant Trend	0.007	NS	NS	NS
Number of IPs	Place patients on ventilators	More IPs more likely to perform component	< 0.001	< 0.001	< 0.001	< 0.001
Number of IPs	Observe adherence and report results to staff for deep venous prophylaxis	Fewer IPs more likely to perform component	NS	NS	0.041	NS
Number of IPs	Place central lines	More IPs more likely to perform component	NS	0.009	NS	NS
Number of IPs	Determine each day if catheter is necessary and remove unnecessary catheters	No Significant Trend	0.015	NS	NS	NS
Laboratory located at hospital	Perform active surveillance testing	No Significant Trend	NS	NS	NS	0.019

[a] NS=Not significant.

[b] Infection preventionist.

Table 5.7: Facilitators that promoted in implementing the Institute for Healthcare Improvement's MRSA bundle components (N = 330)

Facilitator	**Number of Responses (%)**
Support from within the hospital	111 (34)
A specific intervention[a]	64 (19)
Capability to identify patients that are colonized with MRSA	35 (11)
Influence of guidelines or regulations	22 (7)
Desire to educate healthcare workers and families	22 (7)
Desire to improve patient safety within their hospital	14 (4)
Decision to decrease the transmission of MRSA within their hospital	7 (2)
Awareness that MRSA rates increased at their hospital	7 (2)
Desire to prevent hospital-associated infections within their hospital	7 (2)
Awareness of MRSA rates within the community	6 (2)
Other	35 (11)

[a] Such as hand hygiene, contact precautions, and active surveillance culturing.

Table 5.8: Barriers that hindered implementation of the Institute for Healthcare Improvement's MRSA bundle components (N = 318)

Barrier	**Number of Responses (%)**
Lack of support	87 (27)
Poor adherence among healthcare workers	63 (20)
Inadequate funding	34 (11)
Lack of time to implement components	31 (10)
Lacked of resources to implement bundle components at the level of the hospital or the infection prevention program	24 (8)
Inadequate knowledge among staff about infection prevention policies and guidelines	21 (7)
Lack of electronic medical record or the inability to flag MRSA positive patients easily	13 (4)
Perception that MRSA was not a problem within their hospital because rates of MRSA infections were low	12 (4)
Hospital lacked standard infection prevention guidelines within their hospital	8 (3)
Problems with environmental cleaning	6 (2)
Other	19 (6)

CHAPTER 6

DISCUSSION

Summary of Current Projects

The first project identified risk factors for mortality and extended length of stay in the hospital among patients with MRSA pneumonia. None of the microbial characteristics were significantly associated with either mortality or increased length of stay. Age, hospital-onset pneumonia, and admission to ICUs were predictors for both mortality and increased length of stay. Additionally, receiving vancomycin was associated with increased length of stay. These predictors are potentially correlated with severity of illness. Generally, severely ill patients are admitted to the ICU, and they are at risk of developing hospital-onset infections due to their weakened immune systems. Furthermore, severely ill patients can die from underlying comorbidities before antimicrobials inhibit the organisms causing the infections.

The original goal of the first project was to examine a cohort of patients who had MRSA pneumonia and who were either coinfected or previously infected with influenza. However, we identified only 8 (8/23) patients who had laboratory-confirmed influenza. A retrospective study may not be appropriate for identifying patients who had influenza and a secondary or coinfection with MRSA pneumonia because medical records often did not indicate if the patient had influenza and many patients were not tested for the influenza virus during their admissions. Therefore, we changed focus of the study to MRSA pneumonia.

The second project compared empiric treatment with β-lactams versus vancomycin and definitive treatment with β-lactams versus vancomycin among patients with MSSA bacteremia admitted to a Veterans Affairs (VA) Medical Center. We found that receiving empiric treatment with a β-lactam was associated with death. However, we observed a protective effect for patients who received empiric treatment with an antistaphylococcal penicillin or a first generation cephalosporin compared with

vancomycin. Additionally, the hazard for mortality was higher for patients who were younger and healthier compared with patients who were older and sicker when stratifying on age and APACHE III score. We postulate that young, healthy patients have an enhanced innate immune response to the bactericidal effect of the β-lactam. However, a protective effect occurred among patients that received definitive treatment with a β-lactam compared with vancomycin. Additionally, the association remained for patients who received an antistaphylococcal penicillin or a first generation cephalosporin compared with vancomycin for definitive treatment of their MSSA bacteremia. This study supports the recommendation by the Infectious Diseases Society of America (IDSA) to treat patients who have MSSA bacteremia with antistaphylococcal penicillins or first generation cephalosporins once the susceptibility results are available (152).

The third project described the interventions Iowa hospitals implemented to prevent hospital-onset MRSA infections. Our results suggest that these hospitals may not have the support and funding for implementing interventions and/or monitoring adherence to important infection prevention interventions and, thus, may have difficulty preventing the spread of MRSA. This finding is important because many patients admitted to hospitals reside in nursing homes, and nursing home residents are at high risk of carrying MRSA and other resistant pathogens (202-204). If hospitals can prevent MRSA transmission and infections, they can decrease the likelihood of discharging patients who carry multidrug resistant organisms into communities. This would reduce the spread of these organisms and, thereby, improve the health and quality of life for persons living in these communities.

Our study facilitated these efforts by providing benchmark data regarding implementation of the IHI MRSA bundle. Infection prevention staff in hospitals throughout the U.S. can compare their infection prevention practices with the practices implemented within Iowa hospitals. For example, infection preventionists, particularly those at critical access hospitals, could compare their hospitals' practices with respect to

active surveillance for MRSA with the dominant practice in Iowa--active surveillance of specific patient populations--and then assess whether their current practices are optimal for their setting. Infection prevention staff can also use the results of the study to support requests for the resources needed to implement bundle components in their facilities. For example, they can request that hospital administrators and key physicians actively support the implementation.

Limitations to Current Projects

The first project had a few limitations. First, neither center provided data to calculate a severity of illness score. We hypothesize that severity of illness differs between the patients with MRSA pneumonia who died compared with the patients who survived because ICU admission was associated with mortality, and ICU admission could be a marker for severity of illness. Therefore, severity of illness might be an additional predictor for mortality or increased length of stay. Furthermore, severity of illness could be a confounder. For example, patients who are severely ill due their MRSA pneumonia and other comorbidities might be more likely to receive treatment with vancomycin rather than with other antimicrobials like linezolid. Another limitation is that we did not include all patients with MRSA pneumonia in the study cohort because we initially identified patients based on symptoms consistent with influenza-like-illness, such as cough, sore throat, and fever. We did not include patients who had pneumonia, but who did not have these symptoms in the initial cohort.

An additional limitation to this study is the small sample size, which may explain the lack of statistically significant associations between microbial characteristics and poor outcomes. However, this study is one of the largest studies to examine microbial characteristics and poor outcomes among patients with MRSA pneumonia. Many studies examining these characteristics are case series, case reports, or studies involving animal models (118, 119, 122, 176, 205). Case studies and case reports are not adequate for complex analyses because they usually include only a small group of patients that have a

common diagnosis or outcome. Additionally, animal models can be helpful when investigating a specific virulence factor since animals can be infected with mutated strains. However, the outcomes in animal models may not be applicable to people, and mechanisms of pathogenesis may differ between animals and humans.

The main limitation to the second project is that patients could have been classified incorrectly into the empiric or definitive treatment groups based on our cutoff day. Ideally, we would have examined each patient's record to determine when their antimicrobial treatment was changed during their admission. Because our cohort included over 11,000 patients, this method was not feasible. We selected a cutoff of four days based on the proportion of patients within each category per cutoff day and on the average time elapsed after the cultures were obtained until the susceptibility results were available. However, physicians could have switched the antimicrobial treatment before receiving the susceptibility results, or the clinical lab could have used a rapid PCR-based method to identify MSSA thus leading us to misclassify some treatment courses.

Another limitation to the second project is that we performed a retrospective study instead of a prospective study. Therefore, information on a few variables was not available from both hospitals. Furthermore, the variables that were not available may have confounded the association between treatment and mortality. For example, we did not examine differences in healthcare workers' practice patterns or whether patients had infectious disease consults. It is possible that patients with better outcomes were seen by infectious disease physicians.

As mentioned in Chapter 5, a main limitation of the third project is that identification numbers were not included on the surveys. Therefore, we could not analyze changes in prevention practices at an individual hospital over the study period. Additionally, we do not know if the bundle components directly affected infection rates because we did not collect rates overtime from each hospital. If we had collected hospital-onset infection rates, we may not have had adequate statistical power to

associate specific interventions with MRSA reduced infection rates. Furthermore, the results of this study may not be generalizable to all hospitals since many of the participating hospitals had < 50 beds and were located in small communities. For example, small rural hospitals have fewer staff than larger hospitals. Therefore, infection preventionists may be able to monitor adherence to interventions easier than infection preventions working at large urban hospitals. Additionally, small rural hospitals may have difficulty flagging the medical records of patients who are colonized or infected with MRSA if they do not have electronic medical records.

Future Projects

For the first project, we performed a retrospective cohort study and did not identify any significant associations between microbial characteristics and poor outcomes. However, a few characteristics such as ACME detection and PFGE type nearly met the significance of the 0.05 level. Therefore, an additional larger study might find significant associations between microbial characteristics and outcomes.

Some patients with MRSA pneumonia may have been excluded from the retrospective study because they did not have banked MRSA isolates. A prospective study would allow investigators to identify more patients with MRSA pneumonia and to save the isolates for molecular characterization because patients would be required to have at least one MRSA isolate from a respiratory or blood culture to be included in the study. However, patients with MRSA pneumonia could be excluded from a prospective study if they did not have a respiratory or blood culture collected. For example, patients would not be included in the study if they were severely ill and died before cultures were collected or if physicians did not order these cultures from some patients, such as patients with mild illness. A prospective study would also allow investigators to collect data on variables, such as chest x-ray results to verify the diagnosis of pneumonia instead of using an ICD-9-CM code for pneumonia.

Vancomycin is a large molecule that does not penetrate well into the lung. Investigators have compared vancomycin with other antimicrobial agents, such as linezolid, for treatment of MRSA pneumonia (153, 154). We did not directly compare treatment with vancomycin and treatment with linezolid since our population had only 17 patients that were treated with linezolid alone rather than not both linezolid and vancomycin. However, treatment with linezolid was not significantly associated with mortality or length of stay while treatment with vancomycin was associated with increased risk of death and with longer lengths of hospital stay than was treatment with linezolid. Other investigators have reported poor outcomes among patients receiving vancomycin for treatment of MRSA infections. A randomized controlled study of 1,184 patients identified nephrotoxicity more frequently among patients treated with vancomycin (18.2%) than among those treated with linezolid (8.4%) and a significantly higher rate of clinical success among patients treated with linezolid than with vancomycin (154). However, the mortality rates were similar in the two treatment groups (154).

Since we identified poor outcomes in patients receiving vancomycin for MRSA pneumonia, and investigators have not determined ideal treatment for MRSA pneumonia, the next step would be to perform a comparative effectiveness study to examine different treatments for MRSA pneumonia. This study could examine ratios of poor outcomes such as mortality, length of hospital stay, or nephrotoxicity in patients with MRSA pneumonia who were treated with linezolid compared with vancomycin. Our current study could be expanded by either increasing the study period or including patients from other hospitals to increase the sample size and facilitate a comparative effectiveness study. Additionally, investigators could conduct a comparative effectiveness study in a large healthcare system such as the VA Medical Centers, which includes 140 hospitals throughout the U.S.

Our analysis of definitive treatment for MSSA bacteremia identified a protective effect for patients treated with a β-lactam compared with patients treated with vancomycin. Similarly, Schweizer et al. reported a decreased hazard of mortality for patients with MSSA bacteremia who received nafcillin or cefazolin compared with patients who received vancomycin (10). Additionally, they identified a 69% lower mortality hazard for patients whose treatment was changed from vancomycin to nafcillin or cefazolin compared with the patients that remained on vancomycin (10). An additional study, which used Cox proportional hazard regression analysis to compare mortality rates for the patients whose treatment was changed from vancomycin to a β-lactam to mortality rates for patients who received only vancomycin, could clarify further the effect of changing treatment. However, we would need to account for the time-varying issue that would occur among the patients whose treatment was changed from vancomycin to a β-lactam since this occurrence would violate the proportional hazards assumption.

For the second project, we compared treatment with a first generation cephalosporin or antistaphylococcal penicillin with vancomycin treatment. Additional comparative effectiveness studies could compare outcomes of patients treated with other classes of β-lactams with outcomes of patients treated with vancomycin to determine if associations differ among β-lactam classes. Also, first generation cephalosporins and antistaphylococcal penicillins are the agents recommended for treatment of MSSA bacteremia. However, some investigators have speculated that treatment with an antistaphylococcal penicillin may be superior to treatment with a first generation cephalosporin. Yet, Paul et al. did not find a significant difference when they compared treatment with cefazolin to cloxacillin for MSSA bacteremia (OR: 0.81; CI: 0.18-3.62). Lee et al. did not identify differences in treatment failure among patients treated with cefazolin or with nafcillin (OR: 1.6; CI: 0.5-5.4) when they performed a propensity score matched case-control study (206, 207). However, both of these studies may have been too small (< 200 patients) to detect statistically significant differences.

Our third project, found that participating hospitals had implemented most of the IHI MRSA bundle components, but the healthcare workers were not monitoring adherence to the components. Future studies should examine monitoring methods for infection prevention practices. If infection preventionists knew which method was most appropriate for their facility, they might be more inclined to monitor infection prevention practices within their hospital. Additionally, infection preventionists could gain support for acquiring and using a monitoring system by presenting data on the system's efficacy to hospital administrators. Investigators could assess monitoring methods by performing an intervention study in which hospitals are assigned randomly to monitoring the intervention or to standard practice. For example, a study designed to evaluate methods of assessing environmental cleaning could compare direct observation of cleaning with the DAZO method of assessing surface cleanliness, with the ATP method of assessing surface cleanliness, and with surface cultures, with the latter serving as the gold standard. In addition to assessing the utility and the accuracy of the monitoring methods, the investigators could assess whether the level of cleanliness is associated with infection rates.

Conclusion

Staphylococcus aureus is an opportunistic pathogen that causes severe invasive infections such as bacteremia and pneumonia. Patients who acquire these infections may have extended hospitalizations and may die. To improve patient outcomes, investigators need to understand which factors are predictors for unfavorable outcomes and what antimicrobial treatment is optimal for *S. aureus* infections. Additionally, infection control methods can prevent *S. aureus* infections among hospitalized patients. Clinicians and infection preventionists can use the information gained from these studies to improve patient care.

APPENDIX A

CHART REVIEW FORM FOR MRSA PNEUMONIA STUDY

Patient Number:_____

CHART REVIEW FORM

Part 1: When was the patient admitted to the hospital for influenza or pneumonia? Please list admission and discharge dates below.

Admit Date (mm/dd/yyyy)	Discharge Date (mm/dd/yyyy)	Admitted to ICU? (Yes/No/Unknown)	Admission Diagnosis

Part 2: Basic Variables of Interest

Gender	Male Female
Age on admission	years
Weight on admission (dry weight on admission, please specify lbs or kg)	lbs/ kg
Height on admission	in/ cm
Was the patient pregnant during that admission?	Yes No
Is the patient currently a smoker?	Yes No
Does the patient have history of COPD?	Yes No
Did the patient receive an influenza vaccine during/just prior to that influenza season?	Yes No
Did the patient have an invasive device (eg, vascular catheter, gastric feeding tube) at time of admission?	Yes No
Did the patient have documentation of prior history of MRSA colonization or infection?	Yes No
Did the patient undergo surgery in the past 12 months?	Yes No
Did the patient undergo dialysis in the past 12 months?	Yes No
Did the patient live in a long term care facility in the past 12 months?	Yes No

Part 3: Hospitalization Characteristics

Did the patient receive mechanical ventilation during present admission(s)? (only need to look for in patients who had been admitted to ICU)	Yes	No
Was the patient ventilated on admission?	Yes	No
Was the patient ventilated >24 hours prior to culture?	Yes	No
Was the patient ventilated 24 hours +/- culture date?	Yes	No
Was the patient ventilated >24 hours after culture date?	Yes	No
Was the patient admitted to the ICU?	Yes	No
If yes, date of ICU admission and discharge (mm/dd/yyyy)	ICU Admission: ICU Discharge:	

Part 4: Outcomes

Did the patient die during the hospitalization?	Yes	No
If yes, date of death (mm/dd/yyyy)		
Was the patient diagnosed with toxic shock syndrome?	Yes	No
Was the patient diagnosed with necrotizing pneumonia?	Yes	No
Is there documentation of vancomycin treatment failure?	Yes	No

Part 5: Severity of Illness Measures

	PART 7.A At admission (when available for APACHE)	**PART 7.B On the day the culture was taken**
Heart Rate		
Date heart rate was measured (mm/dd/yyyy)		
Temperature		
Date temperature was measured (mm/dd/yyyy)		
Blood Pressure		
Date blood pressure was measured (mm/dd/yyyy)		
Respiratory Rate		
Date respiratory rate was measured (mm/dd/yyyy)		
Partial Pressure of Arterial Oxygen		
Hematocrit (UNIT)		
WBC (UNIT)		
Creatinine (UNIT)		
BUN (UNIT)		
Sodium (UNIT)		
Albumin (UNIT)		
Bilirubin (UNIT)		
Glucose (UNIT)		
Arterial PH		
Date lab variables measured (mm/dd/yyyy)		
Urine Output		
Glasgow Coma Score		

Part 6: Medications

What ANTIBIOTICS did the patient receive?		
Antibiotic	Start Date (mm/dd/yyyy)	Stop Date (mm/dd/yyyy)
What ANTIVIRALS (e.g. amantadine, rimantadine, zanamivir, oseltamivir, paramivir) did the patient receive?		
Antiviral	Start Date (mm/dd/yyyy)	Stop Date (mm/dd/yyyy)

Part 7: Microbiology

Please list all *S. aureus* positive sputum, BAL, tracheal or blood cultures		
Date (mm/dd/yyyy)	Culture type (sputum, BAL, tracheal, blood)	MRSA or MSSA?

Part 8: Influenza Data

Date of influenza diagnosis (mm/dd/yyyy)	
Date of influenza test (mm/dd/yyyy)	
What type of influenza was the patient diagnosed with?	A B Unknown
If influenza A, what strain of influenza? (e.g. H1N1, H3N2)	
Did the patient receive multiple influenza tests?	Yes No
If yes please fill out below:	
Date (mm/dd/yyyy)/Result	

Part 9: Validation of *S. aureus* pneumonia

Date of *S. aureus* pneumonia diagnosis (mm /dd/yyyy)	
Did the patient have an X-ray?	Yes No
Did the patient have a CT Scan?	Yes No
Were the X-ray or CT findings consistent with pneumonia?	Yes No Unsure
Did patient undergo bronchoscopy?	Yes No
If yes, when was the bronchoscopy performed? (If more than one please list all dates)	Date (mm/dd/yyyy):
What were the results of the bronchoscopy? (If more than one, please list results by date)	

Other Comments:

APPENDIX B

MRSA BUNDLE SURVEY FROM 2011

Third Follow-up Survey of Iowa's Healthcare Facilities Regarding IHI's 5 Million Lives Campaign
"MRSA Bundle"

5/2011

If > 1 Infection Control Professionals are attending from a single facility, please work together and submit only 1 copy of the survey.

If 1 ICP works at > 1 facility, please either fill out 1 survey PER facility or pick your primary facility and fill out the survey from that perspective

Please check the box to the FAR RIGHT if you implemented this practice since 5/2010

1. Do you **CURRENTLY** conduct active surveillance for patients colonized or infected with MRSA? Please check the 1 best answer:	**Primary Answer**	**Started since 5/2010**
Patients known to have MRSA previously	❑	❑
Specific patient populations (e.g., all pts undergoing total joint replacements)	❑	❑
if yes, which patient populations _____		
All patients on specific units	❑	❑
if yes, which units _____		
All patients	❑	❑
We do **NOT** do surveillance for MRSA (Please go to questions 5 & 6)	❑	

2. If you **DO** surveillance for MRSA, does the laboratory do:		
Cultures	❑	❑
Real time MRSA PCR	❑	❑
Other, please describe _____	❑	

3. If you **DO** surveillance for MRSA, do you obtain specimens:		
On admission only	❑	❑
On admission and weekly thereafter	❑	❑

On admission, weekly thereafter, and at discharge	❑	❑
On admission and at discharge	❑	❑
Other; please describe _____	❑	

4. If you **DO** surveillance for MRSA, do you obtain specimens:

From the nares only	❑	❑
From the nares and sites of previous infections only	❑	❑
From the nares, sites of previous infections, and wounds	❑	❑
From sites of previous infections only	❑	❑
From wounds only	❑	❑
Other; please describe _____	❑	

5. If you **DON'T** currently do active surveillance for patients colonized or infected with MRSA do you plan to start soon? Please check the 1 best answer:

No, we will not do active surveillance for MRSA	❑
Yes, on patients known to have MRSA previously	❑
Yes, on specific patient populations (e.g., all pts undergoing total joint replacements)	❑
if yes, which patient populations _____	
Yes, on all patients on specific units	❑
if yes, which units _____	
Yes, for all patients	❑

6. If you **DON'T** currently do active surveillance for patients colonized or infected with MRSA and you **DO NOT** plan to start doing surveillance cultures, which of the following **BEST** describes why you won't start doing surveillance cultures?

We don't have a problem with MRSA	❑
We don't have enough staff to collect specimens from patients	❑
We don't have the laboratory resources to do the testing	❑
Active surveillance is not an appropriate control strategy for our facility	❑
Our administration is not supportive	❑
Our physicians are not supportive	❑

Other, please describe _____

GENERAL INFECTION CONTROL PRACTICES THAT LIMIT SPREAD OF MRSA

		Please check the box to the FAR RIGHT if you implemented this practice since 5/2010
7. Have you implemented a program to teach healthcare workers about hand hygiene?		
Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	
8. Do you observe adherence with hand hygiene and feed the data back to staff?		
Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	
9. Do you place patients who are **COLONIZED** with MRSA in contact precautions?		
Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	
10. Do you place patients who are **INFECTED** with MRSA in contact precautions?		
Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	
11. If you place patients **COLONIZED OR INFECTED** with MRSA in contact precautions, do you observe adherence with contact precautions and feed the data back to staff?		
Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

12. Do you monitor the effectiveness of cleaning in rooms housing (or that housed) patients with MRSA?

Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

13. If yes to question 12 (you monitor effectiveness of cleaning) do you (CHECK ALL THAT APPLY):

Obtain cultures to ensure the rooms are clean	❑	❑
Observe housekeepers cleaning and feed data back to housekeeping staff	❑	❑
Participate in Dr. Carling's Goo study	❑	❑
Other, please describe _____	❑	

CENTRAL VENOUS CATHETER PLACEMENT

14. Do staff in your facility place central venous catheters?

Yes (Please go to question 15)	❑
No (Please go to question 23 on page 5)	❑

15. Do you require that persons placing central venous catheters use maximal sterile barrier precautions?

Yes (go to question 16)	❑	❑
No (go to question 17)	❑	
No, but we are planning to do so in the near future (go to 17)	❑	

16. If yes to question 15, do you monitor adherence and report data back to staff?

Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

17. Do you require staff to use chlorhexidine skin antisepsis when placing central venous catheters?

Yes (go to question18 on page 5)	❑	❑
No (go to question 19 on page 5)	❑	

No but we are planning to do so in the near future (go to question 19 on page 5) ❑

18. If yes to question 17, do you monitor adherence and report data back to staff?
Yes ❑ ❑
No ❑
No but we are planning to do so in the near future ❑

19. Is the subclavian vein the preferred site for non-tunneled central venous catheters in adults?
Yes (go to question 20) ❑ ❑
No (go to question 21) ❑
No but we are planning to do so in the near future (go to question 21) ❑
20. If yes to question 19, do you monitor adherence and report data back to staff?
Yes ❑ ❑
No ❑
No but we are planning to do so in the near future ❑

21. Do your staff document every day whether the central venous catheter is necessary?
Yes (go to question 22) ❑ ❑
No (go to question 23) ❑
No but we are planning to do so in the near future (go to question 23) ❑

22. If yes to question 21, do you monitor adherence and report data back to staff?
Yes ❑ ❑
No ❑
No but we are planning to do so in the near future ❑

CARE OF PATIENTS ON VENTILATORS

23. Does your facility have patients with ventilators?
Yes (go to question 24 on page 6) ❑
No (go to question 34 on page 7) ❑

24. Do you require staff to keep the head of the bed at ≥ 30 degrees for ventilated patients?

Yes (go to question 25)	❑	❑
No (go to question 26)	❑	
No but we are planning to do so in the near future (go to question 26)	❑	

25. If yes to question 24, do you monitor adherence and report data back to staff?

Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

26. Do you require staff to do "Sedation Vacations" daily for ventilated patients?

Yes (go to question 27)	❑	❑
No (go to question 28)	❑	
No but we are planning to do so in the near future (go to question 28)	❑	

27. If yes to question 26, do you monitor adherence and report data back to staff?

Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

28. Do you require staff to assess ventilated patients' readiness to extubate daily?

Yes (go to question 29)	❑	❑
No (go to question 30 on page 6)	❑	
No but we are planning to do so in the near future (go to question 30 on page 7)	❑	

29. If yes to question 28, do you monitor adherence and report data back to staff?

Yes,	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

30. Do you require staff to order peptic ulcer disease prophylaxis for ventilated patients?

Yes (go to question 31)	❑	❑
No (go to question 32)	❑	
No but we are planning to do so in the near future (go to question 32)	❑	

31. If yes to question 30, do you monitor adherence and report data back to staff?

Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

32. Do you require staff to order deep venous thrombosis prophylaxis for ventilated patients?

Yes (go to question 33)	❑	❑
No (go to question 34)	❑	
No but we are planning to do so in the near future (go to question34)	❑	

33. If yes to question 32, do you monitor adherence and report data back to staff?

Yes	❑	❑
No	❑	
No but we are planning to do so in the near future	❑	

DEMOGRAPHICS

34. What size is your facility?

< 25 beds	❑
25-50 beds	❑
51-100 beds	❑
101-300 beds	❑
301-500 beds	❑
> 500 beds	❑

35. What is the size of the community in which your facility is located?

< 1,000	❑
1,001-10,000	❑
10,001-100,000	❑
>100,000	❑

36. How many infection control professionals does your facility have?

> 0 but < 1 FTE	❑
1	❑
2	❑
3	❑
4	❑
≥ 5	❑

37. Is you facility in Iowa?

Yes	❑
No	❑

38. Does your facility have an **ON-SITE** laboratory that does testing for MRSA?

Yes	❑
No	❑

39. Is your facility (check all that apply):

An acute care facility	❑
A long-term-care facility	❑
A skilled-care facility	❑
A long-term-ACUTE-care facility	❑

40. Is your facility identified as a Medicare Critical Access Hospital?

Yes	❑
No	❑

Do not know ❑

Please go to the next page

41. What are the 3 primary facilitators of implementing MRSA control measures in your hospital?

42. What are the 3 primary barriers to implementing MRSA control measures in your hospital?

43. Over the past four years, have your rates of <u>nosocomial</u> MRSA infections (circle the one best answer):
Increased Decreased Don't know

44a. Are there any MRSA control measures that your facility implemented but subsequently stopped doing (e.g., active surveillance for MRSA carriers or monitoring adherence to environmental cleaning) Yes No Don't know

44b. If yes, what MRSA control measures did you stop and why did you stop doing them (e.g., lack of funding; no evidence for efficacy; physicians opposed the practice)

45. Was there a particular event or circumstance that motivated your facility to focus on infection control measures for MRSA? (e.g., an outbreak, lawsuit, antibiogram, media attention, statewide reporting, etc.)
Yes ❑

If yes, please describe _____

No ❑
Do not know ❑
Not applicable ❑

46. Do you feel that one component of the bundle had a greater impact at reducing MRSA infections compared to the other components?

No ❑
Yes ❑

If yes, please describe _____

Please go to the next page

47. Have you noticed a decrease in the overall rate of nosocomial infections (not just rates of MRSA infections) since implementing components of the bundle? (Please circle)

A. Overall nosocomial infections	Yes	No	Do not know	Not Applicable
B. Overall bloodstream infections	Yes	No	Do not know	Not Applicable
C. Catheter-associated bloodstream infections	Yes	No	Do not know	Not Applicable
D. Ventilator-associated pneumonia	Yes	No	Do not know	Not Applicable
E. Overall surgical site infections	Yes	No	Do not know	Not Applicable
F. Surgical site infections for specific operation	Yes	No	Do not know	Not Applicable

If yes, please describe _____

G. Catheter-associated urinary tract infections	Yes	No	Do not know	Not Applicable
H. *Clostridium difficile* infections	Yes	No	Do not know	Not Applicable

I. Vancomycin-resistant *Enterococcus* infections	Yes	No	Do not know	Not Applicable
J. Vancomycin-resistant *Enterococcus* colonization	Yes	No	Do not know	Not Applicable
K. MRSA colonization	Yes	No	Do not know	Not Applicable

48. What organism is the leading cause of nosocomial infections at your facility? (Please circle)

Methicillin-resistant *Staphylococcus aureus*

Methicillin-susceptible *Staphylococcus aureus*

Vancomycin-resistant *Enterococcus*

Clostridium difficile

Gram Negatives (Please describe_____)

Other (Please describe_____)

Thank you for filling out this survey.

Loreen Herwaldt
Jennifer Kroeger

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