Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Name Date

Approval Sheet

Retrospective Validation of Methicillin Resistant *Staphylococcus aureus* Risk Assessment Tool against Nasal PCR screening in Hip and Knee Replacement surgeries

By

Rama V. Thyagarajan

Master of Public Health

Prevention Sciences

_____

Dr. Kenneth Castro

Thesis Committee Chair

_____

Dr. Lama Hsaiky

Thesis Committee Advisor

Abstract Cover Page

Retrospective Validation of Methicillin Resistant *Staphylococcus aureus* Risk Assessment Tool against Nasal PCR screening in Hip and Knee Replacement surgeries

By

Rama Thyagarajan

M.B.B.S, Stanley Medical College, 1988

Internal Medicine Residency, Henry Ford Hospital, 1995

Infectious Diseases Fellowship, 2005

Thesis Committee Chair: Dr. Kenneth Castro

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health in Prevention Sciences

2020

Abstract

Retrospective Validation of Methicillin Resistant *Staphylococcus aureus* Risk Assessment Tool against Nasal PCR screening in Hip and Knee Replacement surgeries.

Objective: Due to aging population and increasing prevalence of obesity, joint replacement surgeries are projected to increase substantially by 2030. Prosthetic joint infections (PJI) occur in about 2 % of patients undergoing joint replacement and methicillin resistant S*taphylococcus aureus* (MRSA) is a serious pathogen causing PJI. Skin and nasal colonization is a risk factor for MRSA infections and nasal polymerase chain reaction (PCR) or nasal culture test is used to assess nasal colonization, so effective decolonization can be performed. We evaluated a five question, patient factor based MRSA risk assessment tool against the nasal PCR methodology.

Methods: Pre-operative orthopedic patients who underwent nasal PCR screening before hip or knee arthroplasty at Beaumont Hospital, Dearborn (BHD) from July 2015 to March 2016 were studied retrospectively. Electronic medical record (EMR) review of demographic information and antibiotic use along with on five patient factors that may predict MRSA colonization was collected. The patient factors studied include diabetes mellitus on insulin, hemodialysis, and hospital stay in the last 90 days before surgery, active hospital stay three days before surgery and prior positive MRSA clinical culture or PCR in the last year. Multi variable logistic regression was used to assess if patient factors were able to predict MRSA colonization against nasal PCR screening as a gold standard.

Results: A total of 751 patients underwent nasal PCR screening, of which 38 (5.1%) were MRSA PCR positive and 162 (21.6%) were methicillin susceptible *Staphylococcus aureus* (MSSA) PCR positive. MRSA positive PCR was the dependent variable and the patient risk factors were independent variables. Multivariable logistic regression showed no correlation between patient factors and positive PCR test. The prevalence of risk factors among MRSA positive and MSSA positive patients were similar. Vancomycin use would decrease from 13.7% (with implementation of risk assessment tool) to 5.9 % pre operatively with implementation of nasal PCR screening.

Conclusions: MRSA risk assessment tool did not co relate well against the nasal PCR test to indicate nasal MRSA colonization.

Cover page

Retrospective Validation of Methicillin Resistant *Staphylococcus aureus* Risk Assessment Tool against Nasal PCR screening in Hip and Knee Replacement surgeries

By

Rama Thyagarajan

M.B.B.S

Emory University

2020

Thesis Committee Chair: Dr. Kenneth Castro

A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health

In Prevention Sciences

2020

Acknowledgements

I would like to extend my sincere appreciation to Dr. Kenneth Castro for gracefully accepting to be my mentor and providing valuable feedback from concept to completion of the thesis.

I would like to thank Dr. Hsaiky, my friend and colleague who gave me the confidence to complete the thesis and provided guidance whenever needed.

I would like to thank Dr. Juan Leon for his consistent valuable guidance from discussion of ideas for thesis to completion of the entire project. I am very appreciative of his reassuring personality, and unwavering support.

I would like to thank Dr. Kelley Chester for guiding me through the methods and results section.

I would like to thank Ms. Julie Sobolik for meticulous guidance on proper writing and formatting of the thesis.

I would like to thank my spouse and our children who supported me during my busy schedule for the past 2 years.

Table of contents

Illustrations

Introduction

The increase in osteoarthritis in an aging population (Roberts, 2018), compounded by the obesity epidemic (Inoue, August, 2018) in the United States (US), has created a large population with severe or end stage osteoarthritis. Hence, knee replacement is the most common orthopedic surgical procedure done in the United States (Fingar KR (Truven Health Analytics), December 2014). About 700,100 inpatient knee replacement procedures were completed in 2012, (223 procedures/100,000 population) making this procedure the most commonly performed among hospitalized patients. Also, the number of inpatient stay, partial and total hip replacements was 468,200 (149 procedures/100,000 population) in 2012 making this procedure the fourth most commonly performed in US hospitals (Fingar KR (Truven Health Analytics), December 2014). Most patients recover well, but serious infections of the joint can occur in about 2% of patients (Tande & Patel, 2014) and are categorized as prosthetic joint infections (PJI). The majority of PJI require additional surgical revisions, prolonged treatment with antibiotics and multiple hospitalizations with consequent protracted recovery lasting months to years ((Tande, Gomez-Urena, Berbari, & Osmon, 2017)).

Due to significant number of procedures, knee replacements which are also referred to as arthroplasties add a significant cost burden to the US. The US inpatient cost for total hip arthroplasty (THA) and total knee arthroplasty (TKA) are $23 billion and $50 billion, respectively (Kapadia et al., 2014) (S. M. Kurtz, Lau, Watson, Schmier, & Parvizi, 2012). Accordingly, the total number of hip and knee PJI are projected to increase to 221,500 cases per year by 2030 at an estimated cost of 1.62 billion US dollars (S. Kurtz, Ong, Lau, Mowat, & Halpern, 2007; S. M. Kurtz et al., 2012).

Several bacterial pathogens cause prosthetic joint infections of which methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin susceptible *Staphylococcus aureus* (MSSA) are the most serious causes of PJI and mortality (Tande & Patel, 2014). In 2011, MRSA accounted for 80,461 severe infections and 11,285 deaths in the US (Malani, 2014). MRSA can cause post-operative surgical infections after joint replacement (Torres & Sampathkumar, 2013) (S. M. Kurtz et al., 2012). MRSA PJI has higher morbidity, failure of prosthesis and deaths compared to non-*Staphylococcus aureus (S. aureus)* infections (Hirakawa, Stulberg, Wilde, Bauer, & Secic, 1998). The authors also report that the chances of prosthesis success after PJI are 66.7% if the pathogen was MRSA and around 80% for other pathogens.

Nasal and skin colonization with MRSA increases the risk of PJI (Levy, Ollivier, Drancourt, Raoult, & Argenson, 2013). An average of 15-23% of the orthopedic population has nasal colonization with MSSA and around 1-4% have nasal colonization with MRSA (Moroski, Woolwine, & Schwarzkopf, 2015). Even though several standardized protocols exist to minimize risk of PJI in the pre-operative, peri-operative and post-operative periods, infection prevention experts recommend additional strategies such as nasal MRSA/MSSA screening for all patients prior to undergoing joint replacement procedures. This recommendation to routinely perform pre-operative nasal screening is strong if hospitals have higher than expected rates of *S. aureus* joint infections despite following standard evidence-based practices (Allegranzi et al., 2016; Anderson et al., 2014).

One strategy focuses on MSSA and MRSA screening prior to surgery. If screening is positive for MRSA, subsequent nasal decolonization with intranasal mupirocin along with appropriate MRSA specific antibiotic prophylaxis before elective hip and knee replacement is effective in reducing infections. This is standard practice in many hospitals in the US as

recommended by the American Society of Orthopedic Surgeons, Society of Health care Epidemiologist (SHEA) Surgical site prevention update, and the World Health Organization (WHO) (Allegranzi et al., 2016; Anderson et al., 2014).

Investigation into patient factors that predict MRSA colonization have found that certain patient factors such as history of diabetes, renal dysfunction, recent antibiotic use, recent hospitalization, nursing homes or long term care hospital stay, incarceration in the past 12 months, HIV infection, diagnosis of skin or soft tissue infection upon admission, and past history of MRSA have been described in literature as risk factors for MRSA colonization (Eseonu, Middleton, & Eseonu, 2011; Hidron et al., 2005; Walsh et al., 2018). MRSA nasal screening with culture or polymerase chain reaction (PCR) is currently used to identify MRSA colonization, adding cost, time, process set up and may not be feasible in all hospitals (Beam & Osmon, 2018). If MRSA nasal colonization can be identified through clinical risk assessment tools preoperatively, this can assist providers with decolonization efforts without the need for testing.

Problem statement

MRSA can cause serious infectious complications in patients colonized with MRSA undergoing joint replacement. Current methods for identifying preoperative MRSA colonizers involve nasal screening with added burden of additional staff, access to laboratory diagnostic tests, decolonization medication costs, along with additional time and patient scheduling commitments prior to surgery.

Purpose statement

There is need for an inexpensive, accurate tool to predict MRSA colonization without relying on nasal PCR or culture results.

Primary objective of this work is to:

Validate a MRSA risk assessment tool for MRSA screening using a retrospective chart review of elective orthopedic surgery patients against available MRSA nasal PCR results in patients undergoing hip and knee arthroplasty at Beaumont Hospital, Dearborn, Michigan.

The secondary objectives are to:

a) Evaluate whether vancomycin use has decreased after switching to PCR screening in comparison to the MRSA risk assessment tool.

b) Evaluate the prevalence of risk factors in MRSA colonized patients versus the non-colonized patients.

Research hypothesis

Null hypothesis: The pre-operative MRSA risk assessment tool is not different than the nasal culture or PCR in identifying MRSA nasal colonization in the orthopedic population, undergoing hip or knee replacement.

Alternate hypothesis: The pre-operative MRSA risk assessment tool is worse or better than the nasal culture or PCR test in identifying MRSA nasal colonization in the orthopedic population, undergoing hip or knee replacement.

Significance statement

Despite low rates of PJI, due to high volumes of joint replacement surgeries, PJI add significant costs to the US health care system, significant patient suffering and loss of productivity (Beam & Osmon, 2018; Tande & Patel, 2014). Cost effectiveness studies have clearly validated the need to identify surgical patients colonized with MRSA (Schulz, Nonnenmacher, & Mutters, 2009). Several hospital systems in the US and other countries may

not have timely access to MRSA nasal screening for their orthopedic population. This study will determine if the MRSA risk assessment tool can be used to accurately identify MRSA colonized orthopedic patients as compared to nasal screening methodology.

Definition of terms

B lactam antibiotic: Commonly used group of effective antibiotics with a β lactam ring.

Cefazolin; vancomycin; clindamycin: Commonly used antibiotics to prevent infections after surgery.

Diabetes mellitus: A metabolic disease that causes high blood sugar due to lower production of insulin from the pancreas. High blood sugar increases the risk of infection.

Hemodialysis: A procedure with use of special machine to assist people eliminates toxins as the kidney ceases to function.

Hip and Knee arthroplasty: Surgery on the hip or knee done to replace damaged cartilage or bone where an artificial joint is created with ceramic or metal (prosthesis) and inserted inside the joint.

MRSA/MSSA nasal PCR test: A swab obtained from the nose is processed in a Clinical Laboratory Amendments (CLIA)-certified laboratory using specialized equipment. The test will amplify specific nucleic acid or genetic material to simultaneously detect the gene encoding for methicillin resistance and species confirmation by an *S. aureus* genomic fragment to identify MRSA and MSSA.

MRSA nasal culture: A swab obtained from the nose is processed in the laboratory for growth and identification of MRSA.

MRSA risk assessment tool: Beaumont Dearborn Pharmacy and Infectious Diseases team created a risk assessment tool using five common patient factors for MRSA colonization based on published evidence. If one patient factor is positive, the patient would be considered to be colonized by MRSA.

Mupirocin: A chemical used as ointment or cream that works locally and kills or inhibits the growth of certain bacteria including MRSA.

Nasal Decolonization: Bacteria that live in body parts (nasal cavity, skin, throat, lungs, elsewhere,) without causing illness are considered "colonizers". Procedures are used to broadly reduce the burden of bacterial pathogens ("decolonization") in the nasal cavity and skin to reduce the risk of infection.

Osteoarthritis (OA): OA is the wear and tear of the joints causing breakdown of joint cartilage and adjacent bones. This progresses with time causing increasing pain or swelling there by causing reduced function and disability.

Povidone Iodine: A topical antiseptic used before and after surgery to disinfect skin or mucous membrane.

Prosthetic Joint Infection: The result of bacteria introduced into the joint during surgery or in the post-operative period causing fever, swelling and serious symptoms that need medical and frequently, surgical care.

Revision arthroplasty: Repair of an artificial joint that may be damaged by infection or wear and tear.

Skin decolonization with chlorhexidine bathing: Use of the chemical, chlorhexidine gluconate to wash the skin thoroughly for elimination or reduction of bacterial bioburden. Bacterial colonization may increase risk of infection to the colonized individual, and decolonization has been shown to reduce this risk.

Literature review

The purpose of the study is to validate preoperatively, a tool for assessing the risk of Methicillin Resistant *Staphylococcus Aureus* (MRSA) infection compared against MRSA nasal polymerase-chain reaction (PCR) testing to identify MRSA colonization in patients undergoing hip and knee replacement at Beaumont Hospital, Dearborn, Michigan. Identification of MRSA colonization can assist to identify people who should be provided effective decolonization and antibiotic prophylaxis pre operatively to reduce joint infections.

The purpose of this literature review is to describe the magnitude and relevance of joint replacement surgeries including cost burden of prosthetic joint infections, introduce key concepts pertaining to MRSA nasal colonization and PCR screening, describe patient factors that indicate MRSA nasal colonization and close with the significance of MRSA infection risk assessment tool validation using patient factors.

Joint replacement is the most commonly completed surgical procedure in US hospitals (Fingar KR (Truven Health Analytics), December 2014). The goal of joint replacement is to reduce pain, and suffering; thereby, improving functional independence and quality of life. Due to increased life expectancy and advances in surgical expertise, the number of joint replacements is expected to increase in the US (S. Kurtz et al., 2007). In the US, 468,000 total hip and 700,100 total knee arthroplasties were performed in 2012 (Fingar KR (Truven Health Analytics), December 2014). Studies conducted by Kurtz *et al* (2007) estimate that the annual volume of total knee arthroplasties (TKA) will reach 1.37 million by 2020 and 3.48 million by 2030. The annual volume of primary total hip arthroplasties (THA) is estimated to reach 511,000 by 2020 and 572,000 by 2030 (S. Kurtz et al., 2007). In addition to primary arthroplasties, revision

arthroplasties are also increasing and total hip revisions projected to grow by 137% and total knee revisions projected to grow by 601% between 2005 to 2030 (S. Kurtz et al., 2007). Due to significant surgical advances, joint arthroplasty is a relatively safe procedure with limited failures. Even though a joint prosthesis can have mechanical failure, the most common cause of failure is infection of the joint (Tande et al., 2017). Infection is the most common indication for revision in total knee arthroplasty (Bozic et al., 2010) and the third most common indication in total hip arthroplasty (Bozic et al., 2010). By 2030, the infection risk for hip and knee arthroplasty is expected to increase from 2.18% (S. M. Kurtz et al., 2012) to 6.5% and 6.8%, respectively (S. Kurtz et al., 2007). In addition, owing to increasing risk and the number of individuals undergoing prosthetic joint arthroplasty procedures, the total number of hip and knee prosthetic joint infections is projected to increase to 221,500 cases per year by 2030, at a cost of more than $1.62 billion (S. Kurtz et al., 2007; S. M. Kurtz et al., 2012).

Despite multiple surgeries, if all attempts at surgical control of infection fail, permanent removal of the hardware with placement of an antibiotic cement spacer or fusion of the joint without prosthesis is used to avoid further surgeries. The last resort is amputation of the leg due to intractable knee infections (Haddad, Ngu, & Negus, 2017). With PJI and need for surgeries, patients undergo multiple hospitalizations, rehabilitation at home, outpatient or inpatient rehabilitation facilities and prolonged exposure to many courses of antibiotics (Haddad et al., 2017; Tande & Patel, 2014).

Health care costs related to prosthetic joint infections is significant. Kurtz et al (2012) estimated cost information for hospitalization and revision surgeries utilizing the National Inpatient sample (NIS) database between 2001 and 2009. The NIS database is a large, publically available, all payer, inpatient care database in the US, containing data on more than 7 million

hospital stays each year. The authors reviewed 1,000 hospital based claims data (approximately 20% of US hospitals), based on billing codes and projected PJI cost burden in 2020 with statistical modeling. A total of 159,360 revision arthroplasty procedures due to infection (hip 54,292 and knee 105,068) were completed in 9 years in this nationwide database. Annual infected knee arthroplasties increased from 7,113 cases in 2001 to 14,802 in 2009, while infected hip arthroplasties increased from 4,545 to 7,162 (S. M. Kurtz et al., 2012). The annual infected knee arthroplasties are projected to increase from 17,781 in 2010 to 48,971 cases in 2020 with similar increase in infected hip arthroplasties from 8,136 in 2010 to 16,584 cases in 2020. Using available claims based cost information for hospitalization and revision arthroplasty, the calculated societal cost of PJI in US was 320 million in 2001, 566 million for 2009 and estimated to reach 1.62 billion in 2020 (S. M. Kurtz et al., 2012). Another study reported that in 2005, revision arthroplasty costed 4.8 times greater than primary hip arthroplasty (Haddad et al., 2017). However these cost estimates do not include professional fees for surgeons, anesthesiologists, infectious disease physicians, physical therapists etc. Given the success rate of initial treatment for infection is around 68-90% (Tande et al., 2017), those failing initial surgery will need more surgeries, several hospitalizations, prolonged intravenous antibiotics for months and complex heath care in rehabilitation facilities with a protracted course for months to years, eventually culminating in amputation of the limb in a minority of cases.

In addition to the enormous cost burden of preventable infectious complications after hip and knee arthroplasties, there is significant patient suffering. Chronic pain, deconditioning, inability to return to work or full functional independence, depression, risk of frequent healthcare contact, health care exposure related risk of adverse effects due to many different courses of

antibiotics and other medications, risk of anesthesia, etc., increase the magnitude of the problem (Tande et al., 2017)

MRSA is a common and most serious bacterial pathogen causing PJI (Tande et al., 2017). An analysis of pooled data from 14 studies, including 2,435 patients with PJI, revealed that *S. aureus* (methicillin resistant and methicillin susceptible) was the causative pathogen in 27% of all infections across all time periods and 38% of early infections (less than 3 months) (Tande et al., 2017). MRSA can be a common cause of PJI and studies also report a higher risk of treatment failure if the pathogen involved is MRSA (Salgado, Dash, Cantey, & Marculescu, 2007). The surgical procedure of debridement, antibiotics and implant retention (DAIR) is associated with higher failure rate if the pathogen is *S. aureus* with success rates of only 18-33% (Tande et al., 2017).

Colonization of the skin and mucous membrane can increase the risk of *S. aureus* surgical site infection (SSI). The presence of certain bacteria in body surfaces (nasal cavity, skin, intestine, mouth elsewhere) without causing illness is referred to as colonization. *S. aureus* can be colonized in the skin, peri-anal area and nostrils in certain individuals. Nasal colonization with MSSA is around 15-23%, while colonization with MRSA is around 1-4% in the orthopedic population (Moroski et al., 2015; Neidhart et al., 2018). Skin decolonization with Chlorhexidine gluconate (CHG) showers at home and CHG wipes in the hospital preoperatively are standard procedures recommended for all patients over the past several years regardless of the colonization status (Hidron et al., 2005; Murphy, Spencer, Young, Jones, & Blyth, 2011).

Several studies link *S. aureus* colonization to risk of surgical site infections (SSI). Gupta *et al* (2011) studied the role of MRSA nasal colonization in all surgeries at the Veterans Administration center in Boston between January 2008 and December 2009. All patients

underwent *S. aureus* nasal screening in the preceding 31 days (mean = 5 days) before surgery. A total of 5,200 patients underwent surgery over 2 years of which, 4238 (82%) were screened for MRSA. About 3 of the 279 patients (1.08%) who screened positive for MRSA had surgical site infection (SSI) in comparison to 6 of 3,959 patients (0.15%) of those who screened MRSA negative and had SSI. The weakness of the study is that it is of retrospective, observational design; single hospital study, primarily involving male veterans (91% male) and findings may not be generalized to other populations. Also the number of patients with MRSA SSI was small (Gupta, Strymish, Abi-Haidar, Williams, & Itani, 2011).

Another prospective observational cohort study was conducted in 2,433 patients who underwent orthopedic surgery from April 2003 to June 2005. Patients were screened for MRSA by nasal culture and followed for 26 months prospectively without decolonization efforts. A total of 63 out of 2,433 patients (2.6%) were MRSA nasal carriers. After a minimum of one year follow up, 15 patients developed MRSA SSI; of which 4 out of 63 were MRSA positive carriers and 11 out of 2,360 were MRSA negative non carriers (adjusted odds ratio of 11; P= 0.001) indicating that MRSA colonization is a risk factor for SSI. No phenotyping of the isolates were done to ensure that the strain causing SSI was the same strain that the patient was colonized with (Yano et al., 2009).

MRSA and MSSA colonization can also increase the risk of infections after joint arthroplasty. A retrospective chart review of 3,297 patients who underwent total joint arthroplasty who were screened with nasal culture for *S. aureus* were compared to 1,751 patients who underwent total joint arthroplasty who were not screened for *S. aureus*. The group undergoing screening received nasal decolonization and appropriate antibiotics. Patients in both groups underwent skin decolonization with CHG pre-operatively. At one year follow up,

screened and decolonized patients were 50% less likely to require revision arthroplasty for infections but the number of infections were small (P=0.04) (Malcolm et al., 2016). Levy et al (2013) conducted a meta-analysis of five studies of the benefit of skin and nasal decolonization on surgical infections after orthopedic surgery. The authors concluded that the presence of nasal colonization with *Staphylococcus aureus* (both MSSA and MRSA) increased the risk of surgical site infection after orthopedic surgery (odds ratio of 5.92) but the results of the meta-analysis did not show that nasal decolonization with mupirocin reduced *S. aureus* SSI in the orthopedic subgroup due to lack of power (OR=0.60, 95% CI (0.34-1.06); P=0.08) (Levy et al., 2013).

Nasal culture and nasal polymerase chain reaction (PCR) testing are different methods available for *S. aureus* nasal screening with pros and cons for each. Culture methodology involves both non-selective media and selective media such as chromogenic agar that assist in faster bacterial identification once growth occurs. Cultures plates are inexpensive, but have additive cost of laboratory personnel time, and results can take up to four days to finalize. PCR testing involves amplification of fragments of bacterial nucleic acid or genetic material. This method is faster, considered more expensive than cultures and is not available in all hospitals. Snyder et al (2010) compared culture against PCR methodology and found that a 97% concordance exists between them. The authors also note that PCR had 100% sensitivity, 78% specificity, 70% positive predictive value (PPV) and 100% negative predictive value (NPV). The time to positive PCR was 17.4 hours; whereas the time to positive culture was 28.1 hours. The time to negative PCR was 14.4 hours and the time to negative culture was 51.3 hours (Snyder, Munier, & Johnson, 2010). Yam et al (2013) compared chromogenic agar cultures against PCR methodology. The results showed that chromogenic agar had sensitivity of 84.5%, specificity of 100%, PPV of 100%, and NPV of 97.5% as noted whereas PCR had sensitivity of 76.4%,

specificity of 98.6%, PPV of 89.9% and NPV of 96.3% (Yam et al., 2013). PCR methodology appears to perform as well as selective cultures in all cases with a significantly decreased test turnaround time making it the preferred methodology for nasal *S. aureus* screening. Nasal PCR tests or nasal cultures with selective media are routinely used to test for nasal colorization of MRSA in the last decade. Some PCR equipment only screen for MRSA, whereas others screen for both MRSA and MSSA. Screening for all *S. aureus* is preferred as nasal decolonization with mupirocin or povidone iodine can be applied preoperatively to eliminate nasal colonization.

Proper choice of antibiotic, timing, and adequate dosing of antibiotics pre-operatively is an essential step to reduce joint infections. The Infectious Diseases Society of America (IDSA) and American Society of Hospital Pharmacists (AHSP) have worked collaboratively to develop guidelines for appropriate use of preoperative antibiotics before all procedures (Bratzler et al., 2013). The primary antibiotic recommended before arthroplasty is cefazolin (a β lactam antibiotic). If patients are allergic to β lactam antibiotics, the alternatives that are commonly recommended include clindamycin or vancomycin. If patients are colonized with MRSA, intravenous (IV) vancomycin is the preferred preoperative antibiotic. Vancomycin IV also requires prolonged infusion time of 120 minutes before incision time, making timely completion a challenge. However pre-operative IV vancomycin is recommended if the individual has known MRSA colonization, or if MRSA colonization is suspected or the surgical center has high rates of methicillin resistant infections (Bratzler et al., 2013).

Several studies have looked at patient factors that are predictive of MRSA colonization in different patient populations. A descriptive review of 27 studies identified and stratified patient level risk factors for MRSA colonization (Forster et al., 2013). The authors identified 31 patient level risk factors in 68,777 patients with 2928 cases of MRSA colonization at the time of

hospital admission. The studies either reviewed medical records or included patient questionnaires and sometimes both to study patient factors. The site of MRSA colonization was in the nostrils alone in ten studies and the rest included cultures of wounds, catheter sites, peri-anal areas, and elsewhere. MRSA colonization was identified using culture, PCR and latex agglutination tests. Previous admission to the hospital was included as a risk factor in 25 out of 27 studies; of which, 16 unique risk factor definitions were utilized and 15 studies reported significant association in a multivariable model. Prior antibiotic use was included as a risk factor in 24 studies with 14 unique risk factor definitions and nine studies found significant statistical association in a multivariate model. Previous MRSA colonization was included as a risk factor in eleven studies, with six unique risk factor definitions and 4 studies noted significant association in a multivariable model. Renal failure was included in twelve studies with two unique risk factor definitions and one analyzed study had significant association in a multivariable model. Diabetes mellitus was included as a co-morbid condition in 12 studies with two different definitions of patient risk factors and one study that was analyzed showed significant association in multivariable model. The authors note that due to significant variation in the study population, MRSA colonization testing methodology and risk factor definitions, a meta-analysis could not be conducted (Forster et al., 2013).

Mckinnell et al conducted a literature review with meta-analysis of studies from 1966 to 2012 and found 29 articles on risk factors for MRSA colonization on admission to hospital or intensive care unit (ICU) that included 76,913 patients. Of the 29 studies, 13 were from Europe, 11 from North America, four from Asia and one from Australia. In this meta-analysis, the authors concluded that the following patient risk factors had the highest risk of MRSA colonization; hospital stay in last year (OR: 2.4, $P<.01$); transfer from the Nursing home (OR:

3.8, P<.01); history of MRSA colonization in the last 6 months (OR:14.4,P<.01); anytime MRSA colonization (OR: 8.0, P<.01); recent antibiotic use in the last 90 days (OR of 3.33, P<.01); chronic renal failure on hemodialysis (OR: 1.5, P<.01) and diabetes (OR: 2.30, P<.01*)* (McKinnell, Miller, Eells, Cui, & Huang, 2013).

Patient factors predictive of colonization have also been studied in the orthopedic surgical population. Walsh et al (2018) sought to study patient factors in patients colonized with *S. aureus* during pre-operative screening. A retrospective chart review was conducted on 716 patients undergoing primary or revision of hip or knee arthroplasties who were screened for *S. aureus* with preoperative nasal culture for decolonization. They found that 17.5% of nasal swabs were positive for MSSA, and 1.8% was positive for MRSA. By bivariate analysis, diabetes mellitus (DM), renal insufficiency and immunosuppression were predictive of *S. aureus* nasal colonization; renal insufficiency and immune suppression were independent risk factors for MSSA/MRSA colonization by multi variate analysis (Walsh et al., 2018)

The use of one or more patient risk factors as a tool for pre-operative screening has not been validated in any studies to date. Previous studies have identified several patient clinical factors retrospectively to be statistically significant in a multivariate model (McKinnell et al., 2013). The most common patient factors that were found to be statistically significant in previous studies include, nursing home or long term care residence (active or recent), known MRSA carrier (prior clinical culture or positive screen), presence of devices or open wounds, and hospitalization in the last year (Forster et al., 2013; McKinnell et al., 2013).

A patient factor-based risk assessment tool can be used instead of nasal screening to identify people who are likely colonized with MRSA. The MRSA five question risk assessment tool created at Beaumont Hospital- Dearborn (BH-D) is easy to administer. The five patient

factors included: insulin dependent diabetes mellitus, hemodialysis, prior hospital stay 90 days before surgery, known MRSA carrier or positive culture in the last year and active hospital stay three days prior to surgery. Two of the five risk factors looked at hospitalization status with one indicating short term colonization and the other more indicative of long term colonization. If one question is answered yes, the factor is used as a surrogate to indicate probable MRSA colonization.

If validated, this simple and inexpensive tool can be used in countries where nasal PCR or nasal cultures are not viable options. Hospitals in the US may not have timely access to nasal PCR or nasal culture and if validated, this tool could be useful in emergency orthopedic surgeries where nasal screening cannot be performed. Another benefit to this tool is that it can be administered remotely avoiding another health care visit for preoperative screening. Adoption of MRSA nasal screening protocols involves personnel to test patients, specimen transport and lab processing, follow up on results and subsequently intervention with proper pre-operative decolonization. Several of these steps may be avoided if this risk assessment tool can be used.

To summarize, MRSA nasal colonization is a risk factor for MRSA PJI. Colonization can be identified by nasal screening with culture or PCR but it can be expensive, creates time delay and complex processes and is not convenient. Use of a validated MRSA risk assessment tool that utilizes patient factors to indicate MRSA colonization will be a valuable addition to existing strategies for reduction of prosthetic joint infections.

Problem: MRSA prosthetic joint infections cause significant morbidity with added cost in regards to reoperations, multiple hospitalizations, prolonged intravenous antibiotics and failure of joint prosthesis. Preoperative identification of MRSA colonization through nasal PCR or nasal culture assists with implementation of decolonization protocols and appropriate antibiotic

prophylaxis. However, PCR screening is expensive and requires another patient visit for testing, needs test result follow up and is not available in all medical facilities.

Purpose: A validated MRSA risk assessment tool can be used to identify patients at risk for MRSA colonization and therefore risk of prosthetic joint infection without requiring the additional steps of MRSA screening.

Aim: The purpose of this study is to retrospectively validate MRSA patient factors from patient's medical records against MRSA PCR screening results in patients undergoing hip or knee arthroplasty at Beaumont Hospital in Dearborn, Michigan.

Significance: Validation of the MRSA risk assessment tool can result in an easy and convenient method to identify patients who are at risk for MRSA PJI without needing added tests to identify colonization.

Methods

Institutional Review Board Approvals:

This study received expedited Institutional Review Board (IRB) approval from Beaumont Health (BH) system; the study consisted of a review of existing records and did not involve human subject research interventions. An incoming data transfer agreement was completed by Emory University and Beaumont Health to allow for analysis of de-identified patient data by Dr. Rama Thyagarajan for completion of the thesis requirement as part of the Master of Public Health degree. This study was presented to Emory IRB and was exempt from IRB clearance as only de- identified data are being analyzed.

Beaumont Health Care System:

Beaumont Hospital, Dearborn (BHD) is the second largest hospital within BH's eight hospital system in Southeast Michigan. The hospital has 632 beds and is a teaching and research hospital. The hospital is designated as an orthopedic and joint specialty center with over 1000 joint replacements done in 2019 (internal source from BHD). BHD team voluntarily collects and reports data on hip and knee infections to the National Health Surveillance Network (NHSN) database of the Centers for Disease Control and Prevention (CDC). Beaumont Hospital, Dearborn also participates in Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI), a state-based quality initiative to increase the safety of hip and knee replacements with strong partnership among multiple stakeholders and support by Blue Cross and Blue Shield.

Prior to July of 2015, BHD utilized the MRSA risk assessment tool for elective hip and knee replacement as a proxy indicator for MRSA nasal colonization. Questions were administered during the pre-operative clearance visit in person or over the telephone in the form

of a survey and documented in the pre-operative screening tool in the electronic medical record (EMR) by the pre-anesthesia service nurse completing the visit with the patient. On the day of surgery, the pharmacists had a standing order to determine antibiotic pre-operative choices utilizing EMR documentation for allergy and or the MRSA risk assessment to ensure patients were administered the correct antibiotics. If the MRSA risk assessment was not documented as completed in the EMR, the operating room pharmacist reviewed the patients' electronic medical records and completed the screening based on medical chart, previous history documentations and entered the appropriate antibiotic choice. If the patient was allergic to β lactams or had any one positive risk factor for MRSA, vancomycin was administered. If the allergy or MRSA risk was absent, the patient received cefazolin intravenous (IV) instead to cover for possible MSSA and other skin flora. In addition to the IV antibiotic, nasal decolonization was accomplished by povidone iodine in the pre-operative area on the day of surgery if patients screened positive for MRSA. MSSA nasal colonizers were not identified through the risk assessment tool and did not receive nasal decolonization. All patients undergoing elective hip and knee replacements were instructed on their pre-operative outpatient visit to utilize a CHG skin de-colonization protocol on an outpatient basis prior to surgery, along with education for application regardless of the colonization status. All other pre-operative and operative surgical protocols remained the same for all patients.

After July 2015, BHD replaced the MRSA risk assessment tool with the nasal PCR screening methodology for MRSA pre-operative screening on all patients undergoing elective hip and knee replacements. Patients scheduled for elective hip or knee arthroplasty completed the nasal swabs PCR screening within 21 days prior to surgery. The BD MAX Staph SR machine (FDA approved) was utilized to identify MRSA and MSSA colonization through amplification

of genetic material using PCR methodology with a rapid turnaround time of 24 hours or less. If MRSA or MSSA PCR was positive, the pre-operative nurse applied povidone-iodine into both nostrils on the day of surgery as explained previously. The nostril application was standardized as all nurses underwent training on how to administer the povidone-iodine to ensure consistency among all patients. The surgical clinical pharmacist reviewed the chart the day before and prepared the antibiotic based on patient allergy and colonization status. Dosing and timing of all antibiotics were based on hospital guidelines recommended by the Infectious Diseases and Antibiotic Stewardship Committee and consistent with national guidelines on the dosing, and appropriate timing of antibiotics prior to incision time; vancomycin 15 mg/kg IV for one dose (maximum 2 g) within 60 to 120 minutes of incision time depending on the dose and infusion rate of the drug was provided if indicated for β lactam allergies or MRSA colonization. This retrospective study, conducted in 2018-2019, sought to validate the MRSA risk assessment tool after the PCR nasal screening was introduced.

Patient Population:

All patients scheduled for future elective hip and knee arthroplasty who underwent nasal PCR screening preoperatively at BHD from July 2015 to March 2016 were included if they met eligibility criteria below. This de-identified patient list and data collection tool was stored in a password-protected share point drive only accessible to the primary investigators. An electronic retrospective chart review was conducted by a pharmacy student in 2018-2019 on the entire patient population. BHD was chosen due to the volume of arthroplasty procedures and was the primary site of employment for all investigators. Other hospitals within the health system were not included as either several hospitals performed lower volumes of orthopedic procedures or the investigators did not have full access to the EMR at the time of the study. Patients undergoing

emergent procedures and procedures for infected joints were excluded as they were not tested for colonization. All patients were included in the study only once.

Eligibility criteria: Any adult, ages 18 or older who underwent elective hip or knee replacement at BHD between July 2015 and March 2016 with an MRSA nasal PCR testing was included.

Exclusion criteria: Pregnant women, patients undergoing surgeries due to trauma (non-elective), and any patients with joint infection at time of surgery.

This is a retrospective observational study. A total of 775 patients underwent nasal MRSA screening at BHD between July 2015 and March 2016. Patient lists, date of PCR test and test results were obtained from the microbiology department at BHD. An electronic chart review and collection of specific patient information pertaining to the study was also conducted.

Primary objective:

The primary objective is to validate the MRSA screening questionnaire via a retrospective chart review of elective orthopedic (hip and knee) surgery patients against MRSA nasal PCR results in patients undergoing hip and knee arthroplasty at BHD in Southeastern Michigan from July 2015 to March 2016.

Secondary objective:

a) Evaluate whether vancomycin use has changed after switching to PCR screening in comparison to the MRSA risk factor questionnaire.

b) Evaluate the prevalence of risk factors in MRSA colonized patients versus the non-colonized patients.

After obtaining a list of patients, we used electronic medical records to gather information about individual patients in an excel database. Age, gender, weight, β-lactam

antibiotic allergy, MRSA and MSSA PCR test results, pre and post-operative antibiotic choice and dose of antibiotic were abstracted and recorded. The presence of insulin-dependent diabetes, hemodialysis status, active hospital stay greater three days before surgery, known MRSA carrier or colonizer in the past 12 months, and known health care facility stay prior to the surgery in the last 90 days was included. Any patient with a clinical positive culture or nasal screening was considered a MRSA carrier. Vancomycin use was estimated with application of risk factor tool in this cohort. Cost of vancomycin was calculated based on inpatient pharmacy costs.

Data Analysis:

Descriptive statistics and demographic tables were generated using SAS enterprise Guide 8.1 (Cary, NC). The prevalence of risk factors in the MRSA PCR positive and negative group was calculated using two tailed Fisher exact test. The five MRSA patient factors were analyzed for statistical significance individually and collectively using multivariable logistic regression analysis with Fisher method with outcome variable of interest being the MRSA PCR test. The independent variables studied were the five patient factors included in the risk assessment tool.

Results

Demographics:

Out of the 775 patients who had undergone an elective orthopedic procedure between July 2015 to March 2016, 24 patients were excluded as surgery was canceled after PCR testing or de-duplication. Of the remaining 751 patients that were screened, 162 (21.6%) had a positive PCR test; 38 (5.1%) were positive for MRSA PCR and the rest (16.5%) were positive for MSSA PCR (Figure 1). The majority of PCR positive results were for MSSA PCR (76.5%). Our study did not identify any patients who were both MRSA and MSSA PCR positive.

The mean age of population screened was 67.3 years, with 488 women (65%). Only 38 (5%) of the screened population had diabetes on insulin therapy, 9 (1%) patients overall had known MRSA colonization in the last year, 6 (0.8%) had an active hospital stay more than 3 days before surgery, 3 (0.4%) were on hemodialysis, and 61 (8 %) had prior hospital stay 90 days before surgery.

A total of 561 (74.6%) used cefazolin preoperatively, 60(8%) used vancomycin pre-operatively, 126 (16.8%) used clindamycin preoperatively and these three drugs contributed to nearly 100% of pre-operative antibiotic use. β- lactam antibiotic allergy was noted in 133 /751 (18%) patients. Of the 60 patients receiving vancomycin pre-operatively, 38 were for MRSA nasal screen that was positive, 16 were used as an alternative due β-lactam allergy and six doses were due to surgeon choice.

The total number of patients who screened positive for MRSA by PCR was 38 (5%) and negative for MRSA was 713 (95%). In the MRSA PCR positive cohort, none were on

hemodialysis and no patients had active hospital stay for three days prior to surgery. Two patients were found to be MRSA PCR positive and with insulin dependent diabetes and four patients with positive MRSA PCR had prior inpatient hospital stay in the last 90 days. The MRSA negative study cohort also seems to have similar prevalence of patient factors in the risk assessment tool (Table 3). A known MRSA carrier or positive culture in the last year was the only patient risk factor that suggested a borderline statistical difference (p=0.06) between the MRSA PCR test positive and MRSA PCR test negative groups.

Logistic regression was conducted with the five patient risk factors and none, either individually or combined, were statistically significant (table 4). Insulin dependent diabetes had an OR: 1.0 (P=0.95); Hospital stay in the last 90 days before surgery OR: 1.4 (P=0.53); and known carrier for MRSA OR: 6.4 (P=0.02).

The secondary objective of this study was to assess if vancomycin use decreased after implementation of the MRSA nasal PCR screening. This study showed BHD's pre-operative IV vancomycin use after Jul 2015 was reduced to 5.85%, excluding use for allergies (n=44). With the MRSA risk assessment tool 13.7 % (n=103) would have qualified for pre-operative vancomycin use. The pharmacy cost of vancomycin decreased by 43% in the time-period studied. This is the direct cost avoidance, which doesn't take into account the cost of pharmacy personnel to prepare the medication, storage, nursing time and time needed to administer the medication over 60-120 minutes which might have additional indirect cost avoidance in pre-operative time and personnel and overall cost to the patient.

MRSA risk assessment tool was not validated as a screening tool instead of MRSA nasal PCR screening in this study. However, one patient factor, MRSA carrier or colonization status clearly showed some significance against the PCR method (P=0.02). The prevalence of four

patient factors was similar in both MRSA positive and negative subgroups and known MRSA carrier or positive culture in the last year differed between the two groups (P=0.02). Pre-operative vancomycin use decreased after implementation of the nasal PCR screening tool resulting in marginal direct pharmacy savings, but possibly indirect cost avoidance that was not calculated in this study.

Discussion

Prevention of prosthetic joint infection after hip and knee replacement is a critical step to mitigate significant morbidity and cost (Berríos-Torres et al., 2017; Haddad et al., 2017; S. M. Kurtz et al., 2012). A retrospective observational study was conducted on 751 patients who were screened by PCR methodology between July 2015-March 2016 and presence of pre-determined patient risk factors was reviewed, to validate the MRSA risk assessment tool. We found that patient risk factors either individually or in combination did not accurately predict nasal MRSA colonization. A history of "known MRSA carrier or positive culture in the last year" showed some correlation, but did not achieve statistical importance as a strong predictor of MRSA colonization (P=0.02). The prevalence of risk factors was similar for both MRSA positive and MRSA negative groups except known MRSA carrier or positive culture in the last year which indicated difference but without statistical significance (P=0.06). Pre-operative vancomycin use was lower when nasal PCR screening was used instead of the risk assessment tool, which might lead to the thinking that the risk factor questionnaire might be overestimating the predicted risk of MRSA colonization.

We compared our findings with other similar studies that reviewed patient risk factors that are predictive of *S. aureus* colonization, including studies of patients undergoing orthopedic procedures. In a similar study by Walsh et al, 716 patients undergoing hip and knee arthroplasty were studied retrospectively for *S. aureus* colonization by nasal PCR testing in the preceding six weeks before surgery. About 17.5% of patients were MSSA positive and 1.8% were MRSA positive (Walsh et al., 2018). The authors found that diabetes and chronic renal insufficiency

were predictors of *S. aureus* (SA) colonization by bivariate analysis. Immune suppression and renal insufficiency were independent predictors for SA colonization in multivariate analysis. In comparison, our rates of MRSA were higher (5% vs 1.8%). This study identified some patient level risk factors that were significant by combining both MSSA and MRSA positive patients. Another study by Stapleton et al reviewed patient risk factors for *S. aureus* colonization in 2,147 hip and knee arthroplasty patients. About 3.7% were colonized with MRSA and 23.2% were colonized with MSSA (Stapleton et al., 2020). The authors found that Hispanic ethnicity, immune suppressive medications and revision surgery were independent predictors of MRSA nasal colonization. Torres et al studied MRSA patient risk factors for patients admitted into the hospital and found that nursing home residence, diabetes, hospitalization in the last year and chronic skin conditions were indicative of MRSA colonization (Torres & Sampathkumar, 2013). The patient risk factors like nursing home residence and chronic skin conditions studied are not applicable in the pre-operative orthopedic population. Other risk factors like renal insufficiency and DM are relevant risk factors in both orthopedic populations and in patients admitted to the hospital.

Our study found that the chosen patient risk factors were infrequent and hence not reliable in predicting MRSA nasal colonization. This is consistent with the results by Butler et al, who noted that screening nasal swabs surpassed traditional risk factors as predictors for MRSA bacteremia. The authors retrospectively reviewed 100 patients with MRSA bacteremia between the periods of 2010-2015. Diabetes with or without end stage organ damage, moderate to severe renal insufficiency and inpatient hospitalization in the last 12 months were studied along with many co-morbidities and no patient risk factors were significant in predicting MRSA bacteremia (Butler-Laporte, Cheng, McDonald, & Lee, 2018). However, the previous two studies (Butler-

Laporte et al., 2018; Torres & Sampathkumar, 2013) evaluated non-orthopedic patient populations, which limit the ability to draw comparisons in the pre-operative orthopedic populations.

There may be multiple reasons why our study results showed poor correlation of pre-determined patient risk factors to MRSA PCR results and different than some previous studies. Our study population was overall healthy, with a small percent of diabetes and renal insufficiency requiring hemodialysis. The questionnaire used for MRSA PCR correlation was based on EMR review, which is a limiting factor if patients did not have previous documentation in the EMR. Prior MRSA colonization was shown to be a strong predictor of MRSA colonization in previous cohorts. Our data is dependent on EMR documentation and if a patient had no previous microbiology cultures documented, it was assumed that they were not previously colonized. In addition, our cohort did not look at ethnicity and race to determine correlation.

Different studies predicated different patient risk factors based on different study populations and settings; no risk factor was consistently noted to predict MRSA nasal colonization. Based on prior studies and ours, we recommend PCR or culture-based testing as the only reliable method to identify pre–operative patients colonized with MRSA nasally. Also, given that nasal MRSA culture results take an average of 51 hours instead of the PCR test turnaround of 17 hours, makes nasal PCR testing a preferred option (Snyder et al., 2010).

Our study also assessed vancomycin use with documentation of reduced use by 43% with use of nasal PCR screening test. Reduction in use is important as vancomycin has been documented to be inferior in treatment of MSSA bacteremia, another serious cause of PJI (Chang et al., 2003; Wong, Wong, Romney, & Leung, 2016). Given that MSSA PJI are more common than MRSA PJI, appropriate use of vancomycin only when indicated for MRSA coverage is

important. Use of vancomycin can also contribute to nephrotoxicity given intra operative fluid shift, hypotension, concurrent nephrotoxic drugs, post-operative fluid status and frequent continuation of antibiotics in the immediate post-operative period despite recommendations against routine post-operative antibiotics (Jeffres, 2017). Vancomycin preoperative use creates challenges due to longer infusion time of 120 minutes in comparison to cefazolin which can be administered quickly over few minutes (Bratzler et al., 2013).

One of the potential biases to be addressed is the use of MRSA nasal PCR as gold standard against which the MRSA risk factors are validated. According to BD MAX StaphSR, the test sensitivity is 93%, specificity is 98%, positive predictive value is 76% and negative predictive value is 100%. Given that probability of true MRSA positivity is around 76% by nasal PCR methodology, creates a selection bias of non-representative population being included (BD MAX, 2020).

Our study found no association between the nasal PCR tests and a predetermined list of patient risk assessment tool and hence we do not recommend use of this tool in pre-operative elective orthopedic procedures. In the event of an emergency procedure or inability of the patient to complete nasal screening using PCR or culture based testing, the risk assessment tool should not be used. Future studies should be conducted to explore use of rapid, reliable, sensitive and inexpensive point of care testing once it is available for broad clinical use. Skin decolonization is pre –operatively recommended for all arthroplasty cases, but universal nasal decolonization increases the risk of mupirocin resistance and is therefore not recommended. Test based nasal decolonization can assist with targeted interventions, but may not be feasible in many centers doing arthroplasty. Availability of point of care testing with molecular diagnostic tools to detect markers for MRSA presence in nasal swabs will be beneficial. The authors (van Belkum &

Rochas, 2018) review the need and availability of several non-culture based rapid, diagnostic tools that are in development to identify MRSA and MSSA for point of care testing use. The technologies include polymerase chain reaction (PCR), nucleic acid sequence-based amplification (NASBA), recombinase polymerase amplification (RPA), loop –mediated isothermal amplification (LAMP) and whole genome sequencing (WGS). With availability of MRSA nasal colonization results rapidly in the pre-operative setting, vancomycin antibiotic prophylaxis can be used and intranasal decolonization can occur with povidone-iodine in the pre-operative area.

While use of MRSA risk assessment tool is a novel application, the sample size was too small to find a statistical association due to very low prevalence of patient risk factors. If future studies are conducted larger sample sizes should be used. The authors (Bujang, Sa'at, Sidik, & Joo, 2018) recommend a sample size of 350-500 for observational logistic regression analysis to achieve statistical significance. Based on MRSA population prevalence of around 5%, we estimate that 7,000-10,000 pre-operative patients should be prospectively studied to validate the MRSA risk assessment tool. Future studies with focus on a risk-based score using patient characteristics that could accurately predict individuals who are likely to be nasally colonized with MRSA in the orthopedic population could be considered. If such a study is conducted it should be prospective with large sample size and inclusion of other risk factors like recent antibiotic use, immune suppression that may predict colonization. Even if the risk assessment tool is able to only identify a subset of patients at highest risk for PJI accurately, this tool could be of value in hospitals where PCR tests are not available. However, that risk assessment tool would need to be validated first.

There are several limitations in this study. This was a non - randomized, retrospective, single institution study conducted in the mid-western United States, and may not represent the experience in other institutions elsewhere. An electronic chart review was utilized for data collection and only data available within BHD electronic health records (EHR) were included as present. The major limitation is the small sample size in each risk factor group. Of the 751 total patients, 38 patients had positive MRSA nasal PCR and only eight patients had one risk factor in the risk assessment tool and two risk factors subset had no patients, making that other analysis irrelevant. Given the increasing prevalence of osteoarthritis in the aging population, this study suggests careful patient selection preoperatively to influence outcomes. It may also indicate that patients with several comorbidities may already have significant limitations in activities of daily living that joint replacement is not expected to improve.

The WHO recommends nasal decolonization preoperatively despite acknowledging difficulties for MRSA screening in low- and middle-income countries (Allegranzi et al., 2016). We are not aware of any studies that indicate routine screening for MRSA and MSSA nasal colonization in these countries. A rapid, affordable and reliable point-of-care test based on molecular methods will assist low and middle countries reduce their MRSA and MSSA prosthetic joint infections.

The number of arthroplasty procedures are increasing in the US (S. Kurtz et al., 2007) and PJI are the most dreaded complication of joint arthroplasty. Based on our findings, we recommend the use of PCR methodology over nasal cultures or MRSA risk assessment tool in the pre-operative orthopedic population to perform nasal decolonization in an effort to reduce MRSA PJI. Prospective studies with larger populations of pre-operative patients including additional risk factors like immune suppression, prior antibiotic use, and combination of risk

factors against nasal screening with PCR or culture to seek validation and, most importantly document reduction in PJI could be considered. PCR tests add cost, require resources, and take time and coordination in the pre-operative period. Other inexpensive, sensitive, accurate, point of care tests to rapidly identify nasal colonization pre-operatively once commercially available, would benefit patients when traditional PCR testing related time delay is not acceptable, cannot be implemented or if point-of care testing proves comparable or superior in the future.

Conclusion

In conclusion, the MRSA risk assessment tool evaluated in this study did not correlate well against MRSA PCR test as a surrogate marker for MRSA nasal colonization in pre-operative patients undergoing hip and knee arthroplasty. We recommend ongoing research and better technology to implement point-of-care molecular diagnostic tools that can accurately diagnose MRSA nasal colonization. With rapid and accurate diagnosis of MRSA nasal colonization, the large population of patients who undergo hip and knee arthroplasty will benefit by reduction of prosthetic joint infection.

References

Allegranzi, B., Zayed, B., Bischoff, P., Kubilay, N. Z., de Jonge, S., de Vries, F., . . . Solomkin, J. S. (2016). New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis, 16*(12), e288-e303.

Anderson, D. J., Podgorny, K., Berríos-Torres, S. I., Bratzler, D. W., Dellinger, E. P., Greene, L., . . . Kaye, K. S. (2014). Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol, 35*(6), 605-627.

Beam, E., & Osmon, D. (2018). Prosthetic Joint Infection Update. *Infect Dis Clin North Am, 32*(4), 843-859.

Berríos-Torres, S. I., Umscheid, C. A., Bratzler, D. W., Leas, B., Stone, E. C., Kelz, R. R., . . . Schecter, W. P. (2017). Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg, 152*(8), 784-791.

Bozic, K. J., Kurtz, S. M., Lau, E., Ong, K., Chiu, V., Vail, T. P., . . . Berry, D. J. (2010). The epidemiology of revision total knee arthroplasty in the United States. *Clin Orthop Relat Res, 468*(1), 45-51.

Bratzler, D. W., Dellinger, E. P., Olsen, K. M., Perl, T. M., Auwaerter, P. G., Bolon, M. K., . . . Weinstein, R. A. (2013). Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm, 70*(3), 195-283.

Bujang, M. A., Sa'at, N., Sidik, T., & Joo, L. C. (2018). Sample Size Guidelines for Logistic Regression from Observational Studies with Large Population: Emphasis on the Accuracy Between Statistics and Parameters Based on Real Life Clinical Data. *Malays J Med Sci, 25*(4), 122-130.

Butler-Laporte, G., Cheng, M. P., McDonald, E. G., & Lee, T. C. (2018). Screening swabs surpass traditional risk factors as predictors of MRSA bacteremia. *BMC Infect Dis, 18*(1), 270.

Chang, F. Y., Peacock, J. E., Jr., Musher, D. M., Triplett, P., MacDonald, B. B., Mylotte, J. M., . . . Yu, V. L. (2003). Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore), 82*(5), 333-339.

Eseonu, K. C., Middleton, S. D., & Eseonu, C. C. (2011). A retrospective study of risk factors for poor outcomes in methicillin-resistant Staphylococcus aureus (MRSA) infection in surgical patients. *J Orthop Surg Res, 6*, 25.

Fingar KR (Truven Health Analytics), S. C. A., Weiss AJ (Truven Health Analytics), Steiner CA (AHRQ). (December 2014). Most Frequent Operating Room Procedures Performed in U.S. Hospitals, 2003-2012. (HCUP Statistical Brief #186.).

Forster, A. J., Oake, N., Roth, V., Suh, K. N., Majewski, J., Leeder, C., & van Walraven, C. (2013). Patient-level factors associated with methicillin-resistant Staphylococcus aureus carriage at hospital admission: a systematic review. *Am J Infect Control, 41*(3), 214-220.

Gupta, K., Strymish, J., Abi-Haidar, Y., Williams, S. A., & Itani, K. M. (2011). Preoperative nasal methicillin-resistant Staphylococcus aureus status, surgical prophylaxis, and risk-adjusted postoperative outcomes in veterans. *Infect Control Hosp Epidemiol, 32*(8), 791-796.

Haddad, F. S., Ngu, A., & Negus, J. J. (2017). Prosthetic Joint Infections and Cost Analysis? *Adv Exp Med Biol, 971*, 93-100.

Hidron, A. I., Kourbatova, E. V., Halvosa, J. S., Terrell, B. J., McDougal, L. K., Tenover, F. C., . . . King, M. D. (2005). Risk factors for colonization with methicillin-resistant Staphylococcus aureus (MRSA) in patients admitted to an urban hospital: emergence of community-associated MRSA nasal carriage. *Clin Infect Dis, 41*(2), 159-166.

Hirakawa, K., Stulberg, B. N., Wilde, A. H., Bauer, T. W., & Secic, M. (1998). Results of 2-stage reimplantation for infected total knee arthroplasty. *J Arthroplasty, 13*(1), 22-28.

Inoue, Y., Qin, B., Poti, J., Sokol, R., & Gordon-Larsen, P. . (August, 2018). Epidemiology of Obesity in Adults: Latest Trends. *Current obesity reports, 7(4)*, 276–288.

Jeffres, M. N. (2017). The Whole Price of Vancomycin: Toxicities, Troughs, and Time. *Drugs, 77*(11), 1143-1154.

Kapadia, B. H., McElroy, M. J., Issa, K., Johnson, A. J., Bozic, K. J., & Mont, M. A. (2014). The economic impact of periprosthetic infections following total knee arthroplasty at a specialized tertiary-care center. *J Arthroplasty, 29*(5), 929-932.

Kurtz, S., Ong, K., Lau, E., Mowat, F., & Halpern, M. (2007). Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am, 89*(4), 780-785.

Kurtz, S. M., Lau, E., Watson, H., Schmier, J. K., & Parvizi, J. (2012). Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty, 27*(8 Suppl), 61-65.e61.

Levy, P. Y., Ollivier, M., Drancourt, M., Raoult, D., & Argenson, J. N. (2013). Relation between nasal carriage of Staphylococcus aureus and surgical site infection in orthopedic surgery: the role of nasal contamination. A systematic literature review and meta-analysis. *Orthop Traumatol Surg Res, 99*(6), 645-651.

Malani, P. N. (2014). National burden of invasive methicillin-resistant Staphylococcus aureus infection. *Jama, 311*(14), 1438-1439.

Malcolm, T. L., Robinson le, D., Klika, A. K., Ramanathan, D., Higuera, C. A., & Murray, T. G. (2016). Predictors of Staphylococcus aureus Colonization and Results after Decolonization. *Interdiscip Perspect Infect Dis, 2016*, 4367156.

McKinnell, J. A., Miller, L. G., Eells, S. J., Cui, E., & Huang, S. S. (2013). A systematic literature review and meta-analysis of factors associated with methicillin-resistant Staphylococcus aureus colonization at time of hospital or intensive care unit admission. *Infect Control Hosp Epidemiol, 34*(10), 1077-1086.

Moroski, N. M., Woolwine, S., & Schwarzkopf, R. (2015). Is preoperative staphylococcal decolonization efficient in total joint arthroplasty. *J Arthroplasty, 30*(3), 444-446.

Murphy, E., Spencer, S. J., Young, D., Jones, B., & Blyth, M. J. (2011). MRSA colonisation and subsequent risk of infection despite effective eradication in orthopaedic elective surgery. *J Bone Joint Surg Br, 93*(4), 548-551.

Neidhart, S., Zaatreh, S., Klinder, A., Redanz, S., Spitzmuller, R., Holtfreter, S., . . . Bader, R. (2018). Predictors of colonization with Staphylococcus species among patients scheduled for cardiac and orthopedic interventions at tertiary care hospitals in north-eastern Germany-a prevalence screening study. *Eur J Clin Microbiol Infect Dis, 37*(4), 633-641.

Roberts, A. W., Ugunwole,S.U., Blaklee,L., Rabe,A.M.,. (2018). The Population 65 Years and Older in the United States *American Community Service Reports, 38*.

Salgado, C. D., Dash, S., Cantey, J. R., & Marculescu, C. E. (2007). Higher risk of failure of methicillin-resistant Staphylococcus aureus prosthetic joint infections. *Clin Orthop Relat Res, 461*, 48-53.

Schulz, M., Nonnenmacher, C., & Mutters, R. (2009). Cost-effectiveness of rapid MRSA screening in surgical patients. *Eur J Clin Microbiol Infect Dis, 28*(11), 1291-1296.

Snyder, J. W., Munier, G. K., & Johnson, C. L. (2010). Comparison of the BD GeneOhm methicillin-resistant Staphylococcus aureus (MRSA) PCR assay to culture by use of BBL CHROMagar MRSA for detection of MRSA in nasal surveillance cultures from intensive care unit patients. *J Clin Microbiol, 48*(4), 1305-1309.

Stapleton, E. J., Petrone, B., Zois, T., Papas, V., Frane, N., Green, E., & Scuderi, G. R. (2020). Predictors of Staphylococcus Aureus Nasal Colonization in Joint Arthroplasty Patients. *J Knee Surg*. Tande, A. J., Gomez-Urena, E. O., Berbari, E. F., & Osmon, D. R. (2017). Management of Prosthetic Joint Infection. *Infect Dis Clin North Am, 31*(2), 237-252.

Tande, A. J., & Patel, R. (2014). Prosthetic joint infection. *Clin Microbiol Rev, 27*(2), 302-345.

Torres, K., & Sampathkumar, P. (2013). Predictors of methicillin-resistant Staphylococcus aureus colonization at hospital admission. *Am J Infect Control, 41*(11), 1043-1047.

van Belkum, A., & Rochas, O. (2018). Laboratory-Based and Point-of-Care Testing for MSSA/MRSA Detection in the Age of Whole Genome Sequencing. *Front Microbiol, 9*, 1437.

Walsh, A. L., Fields, A. C., Dieterich, J. D., Chen, D. D., Bronson, M. J., & Moucha, C. S. (2018). Risk Factors for Staphylococcus aureus Nasal Colonization in Joint Arthroplasty Patients. *J Arthroplasty, 33*(5), 1530-1533.

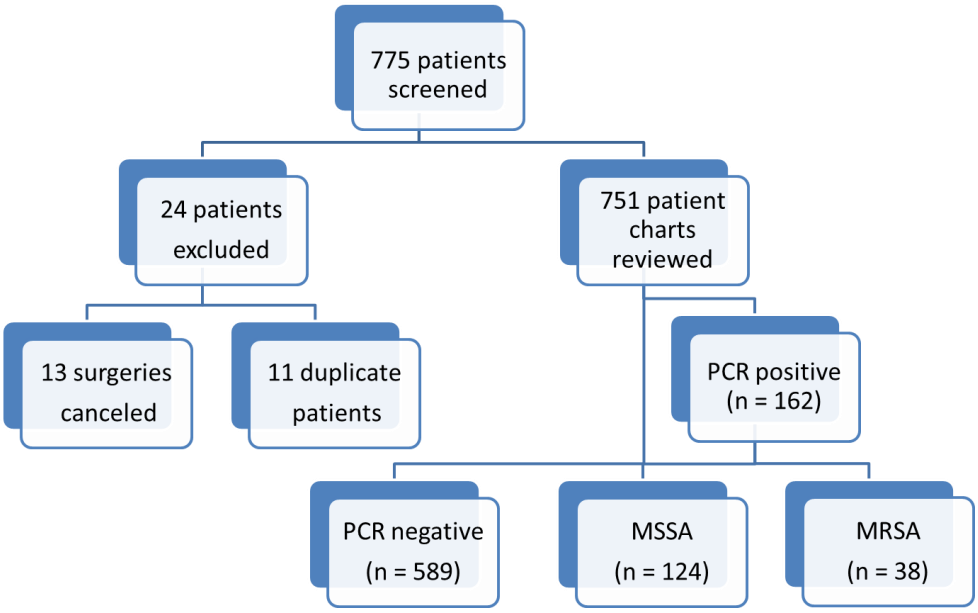
Wong, D., Wong, T., Romney, M., & Leung, V. (2016). Comparative effectiveness of β-lactam versus vancomycin empiric therapy in patients with methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia. *Ann Clin Microbiol Antimicrob, 15*, 27.

Yam, W. C., Siu, G. K., Ho, P. L., Ng, T. K., Que, T. L., Yip, K. T., . . . Yuen, K. Y. (2013). Evaluation of the LightCycler methicillin-resistant Staphylococcus aureus (MRSA) advanced test for detection of MRSA nasal colonization. *J Clin Microbiol, 51*(9), 2869-2874.

Yano, K., Minoda, Y., Sakawa, A., Kuwano, Y., Kondo, K., Fukushima, W., & Tada, K. (2009). Positive nasal culture of methicillin-resistant Staphylococcus aureus (MRSA) is a risk factor for surgical site infection in orthopedics. *Acta Orthop, 80*(4), 486-490.

Figures

Figure 1: Flow diagram of eligible study participants (adults [age >18 years] who underwent elective hip and knee replacement at BHD between July 2015 and March 2016) and PCR results



Tables

Table 1: Risk assessment tool variables assessed to predict MRSA

Insulin dependent diabetes mellitus	Yes/No
Hemodialysis	Y/N
Prior hospital stay 90 days before surgery	Y/N
Known MRSA carrier or positive culture in the last year	Y/N
Active hospital stay three days prior to surgery	Y/N

Y= Yes; N= No

Table 2: Sociodemographic and clinical characteristics of study cohort (adults [age ≥18 years] who underwent elective hip or knee replacement at BHD between July 2015 and March 2016 with an MRSA nasal PCR testing)

Characteristics	Study cohort (n=751) ± SD
Age	67.3 ± 9.9
Weight (kg) or BMI (kg/m^2)	92.7 ± 21.7 or 33.1 ± 7.9
Gender (F)	488 (65%)
Insulin dependent diabetes mellitus	38 (5%)
Hemodialysis	3 (0.4%)
Prior hospital stay 90 days before surgery	61 (8%)
Known MRSA carrier or positive culture in the last year	9 (1%)
Active hospital stay 3 days prior to surgery	6 (0.8%)
PCR results	
MRSA positive	38 (5.1 %)
MSSA positive	124 (16.5%)
Negative PCR results	589 (78.4%)
Preoperative antibiotic given	
Cefazolin	561 (75%)
Vancomycin	60 (8%)
Clindamycin	126 (16.8%)

Table 3: Prevalence of Patient risk factors among MRSA positive and MRSA negative groups

Patient factors	MRSA PCR positive (N=38)	MRSA PCR negative (N=713)	Fisher exact test Pr<=P
Insulin dependent diabetes mellitus	2 (5.3%)	36 (5%)	1.0
Hemodialysis	0 (0%)	3(0.4%)	1.0
Prior hospital stay 90 days before surgery	4 (10.5%)	57 (7.9%)	0.54
Known MRSA carrier or positive culture in the last year	2(5.3%)	6 (0.8%)	0.06
Active hospital stay 3 days prior to surgery	0 (0%)	6 (0.8%)	1.0

Table 4: Logistic Regression Analysis to indicate if any patient factor in MRSA risk assessment tool can predict MRSA nasal colonization by PCR

MRSA patient factors	**Odds Ratio**	**95% CI**
Insulin dependent diabetes mellitus	1.0	0.24 - 4.55
Hemodialysis	<0	-
Prior hospital stay 90 days before surgery	1.4	0.48 - 4.16
Known MRSA carrier or positive culture in the last year	6.4	1.24 - 32.87
Active hospital stay 3 days prior to surgery	< 0	-