Methicillin-Resistant *Staphylcoccus aureus* Infection in a Tertiary Care Hospital in Rural British Columbia: A Retrospective Study of Resistance Patterns and Empiric Antibiotic Therapy

STUDY PROTOCOL

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasingly common human pathogen and an important cause of infection in both hospitalized patients and patients in the community. MRSA refers to the *Staphylococcus aureus* strains that are resistant to beta-lactam antibiotics, including penicillins, cephalosporins, monobactams and carbapenems (1,2). MRSA first emerged in the 1960s after the introduction of the semi-synthetic penicillins, methicillin, oxacillin and cloxacillin, and has since become a common nosocomial pathogen (2). In the United States, it is estimated that 40% of hospital *Staphylococcus aureus* strains are methicillin resistant. In Canada, the rates of nosocomial MRSA are lower than in the United States, with an estimated hospital MRSA rate of 10.4% in 2003 (2). MRSA is often thought of as a hospital-associated infection, however over the past ten years there has been an emergence of genetically distinct MRSA strains in the community setting. These infections have been seen in patients without recent hospitalizations, and are capable of causing infections ranging from mild to life-threatening (2). Thus, regardless of whether the MRSA infection is hospital-associated (HA) or community-associated (CA), it represents an important cause of morbidity and mortality in both the hospital and community settings.

HA-MRSA and CA-MRSA are genetically distinct forms of MRSA and they also differ in terms of the populations they infect and their susceptibility to antibiotics. There are no standardized definitions of HA-MRSA and CA-MRSA. Despite this, however, HA-MRSA is typically defined as MRSA strains that are transmitted to patients within health care facilities (2). There are a number of factors associated with an increased risk of HA-MRSA infection and these include: previous isolation of MRSA, isolation of MRSA more than 48 hours after hospital admission, the presence of an indwelling catheter or percutaneous device at the time of culture, history of hospitalization, surgery, dialysis or residence in a long-term care facility within one year of the MRSA culture date (2).

CA-MRSA is typically defined as MRSA isolates obtained from patients in the community who have not had recent exposure to the health care system and who have none of the risk factors associated with HA-MRSA (2). In addition, CA-MRSA also refers to an MRSA infection in patients in health care

facilities that was present or incubating at the time of admission (2). Certain populations of patients are at higher risk of developing CA-MRSA and these include: young people, Aboriginal or African American individuals, athletes who play contact sports, intravenous drug users, men who have sex with men, those of lower socioeconomic class or living in situations of overcrowding, those with a chronic skin disorder and those with recurrent or recent antibiotic use (2).

Despite the definitions of CA-MRSA and HA-MRSA and the known risk factors for their occurrence, it can often be difficult to determine whether a MRSA infection in a given patient is due to a community or hospital associated pathogen using epidemiologic information alone. This is because hospital strains of MRSA are often found in patients in the community and community strains are often found in hospitalized patients. As such, genetic and antibiotic susceptibility testing are required to definitively determine if a MRSA strain is community or hospital associated. MRSA confers resistance to beta-lactam antibiotics through mutations in the gene that codes for the penicillin binding protein 2a, located in the organism (2,3). There are five different alleles of this gene and each contain different mutations resulting in resistance to beta-lactam antibiotics (2). CA-MRSA and HA-MRSA differ in terms of the genetic mutations found in the gene coding for the penicillin binding protein 2a. CA-MRSA and HA-MRSA also differ in terms of their susceptibility to other classes of antibiotics, aside from beta-lactam antibiotics. In general, CA-MRSA is more susceptible to other types of antibiotics, such as clindamycin, sulfamethoxazole-trimethoprim, fluroquinolone antibiotics and tetracyclines, where as HA-MRSA is resistant to these antibiotics (1,2).

Regardless of whether it is community or hospital-associated, MRSA can result in infections ranging from mild to life-threatening. Common infections caused by MRSA include: skin and soft tissue infections, skin abscesses, osteomyelitis, wound infections, catheter-related infections, pneumonia and bacteremia. The choice of empiric antibiotic therapy in a patient suspected of having an infection caused by MRSA depends on many factors, including the site and severity of the infection, clinical status of the patient, whether the patient developed the infection in the community or in hospital and whether the patient has risk factors for the development of a community-associated or hospital-associated MRSA infection. In general, for mild or moderate infections, such as some skin and soft tissue infections,

suspected to be caused by CA-MRSA, clindamycin, sulfamethoxazole-trimethoprim or a tetracycline antibiotic are reasonable therapeutic alternatives for empiric antibiotic therapy (2,4,5). In those with more severe infections and in patients with risk factors for HA-MRSA, vancomycin is generally indicated (2).

In addition to considering the site and severity of the infection, the patient demographics and clinical characteristics, local antibiotic resistance patterns for MRSA are also important to consider when deciding on empiric antibiotic therapy as they can help guide the choice of antibiotic. HA-MRSA strains are typically resistant to multiple classes of antibiotics, whereas CA-MRSA strains are often only resistant to beta-lactam and macrolide antibiotics (2). As such, more therapeutic options are available for the management of CA-MRSA infections. Despite this, however, resistance to the commonly used antibiotics for the management of CA-MRSA infections can occur and this has the ability to influence the choice of empiric antibiotic therapy for the management of patients suspected of having a CA-MRSA infection.

A study by Moran et al. (6) assessed the susceptibility patterns of MRSA infections in patients presenting the emergency departments in the United States in August of 2004 for skin and soft tissue infections. This study found that for the MRSA isolates, 95% were susceptible to clindamycin, 6% were susceptible to erythromycin, 60% to fluroquinolones, 100% to rifampin, 100% to sulphamethoxazole-trimethoprim and 92% to tetracycline. This study was conducted at University-affiliated hospitals in eleven cities in the United States and due to differences in the prevalence rates of MRSA, the antibiotics used to treat MRSA and the patient populations, the results of this study may not be transferable to centres in Canada and to non-urban centres. Another study conducted at 57 military hospitals and clinics in the United States compared the susceptibility of MRSA cultures obtained from children in 2001-2002 to those obtained from children in 2003-2004 and demonstrated an increase in clindamycin resistance among MRSA cultures from 0.48% in 2001-2002 to 3.97% in 2003-2004 (7). A study by Szumowski et al. (8) assessed the treatment options, clinical outcomes and susceptibility data for MRSA skin and soft tissue infections in an ambulatory clinic in Boston. This study demonstrated that 48.2% of the MRSA cultures were resistant to clindamycin, whereas only 0.5% were resistant to sulfamethoxazole-trimethoprim. These studies provide information on the resistance patterns of MRSA in the hospital and community settings and also highlight some of the differences in resistance patterns at different health

care sites. MRSA resistance to empiric antibiotic therapy depends on antibiotic patterns of use at that health care site, patient clinical and demographic characteristics and microbiologic characteristics of the organism. Therefore, local data on antibiotic patterns of resistance is required to determine the most appropriate empiric antibiotic choice for the management of MRSA infection.

Study Rationale

In British Columbia in 2008, one in five *Staphylococcus aureus* isolates from British Columbia laboratories were methicillin resistant (9). Of these MRSA isolates, 36.2% of them were resistant to clindamycin, 84.8% were resistant to erythromycin, 6.4% were resistant to sulfamethoxazole-trimethoprim and 7.8% were resistant to doxycycline (9). It is unclear from this data, however, how many of these MRSA isolates had the genetic mutations characteristic of CA-MRSA and how many had the genetic mutations characteristic of HA-MRSA.

Kelowna General Hospital serves the city of Kelowna and is also a major referral centre for rural communities in the interior of British Columbia. The incidence of MRSA infections at Kelowna General Hospital is currently not known. In addition, the resistance patterns of MRSA infections at Kelowna General Hospital are also not known. Due to the diverse patient population served by this hospital, it is unclear if the province-wide MRSA susceptibility data can be applied to MRSA infections in Kelowna. As such, a study is required to characterize the susceptibility patterns of MRSA cultures at Kelowna General Hospital and the choice of empiric antibiotic regimens used to treat MRSA infections in this hospital. The purpose of this study will be to provide valuable information on the patterns of resistance for MRSA infections in Kelowna and the demographics and clinical characteristics of the patients infected with MRSA in the interior of British Columbia. In addition, we would like to characterize the current empiric antibiotic choice used for suspected MRSA infections at Kelowna General Hospital.

Study Objectives

Primary Objective

- To characterize the susceptibility patterns of MRSA cultures at Kelowna General Hospital over a one year period

Secondary Objectives

- To characterize the types of infections caused by MRSA at Kelowna General Hospital
- To describe the patient-specific MRSA risk factors, if present, for patients diagnosed with a MRSA infection at Kelowna General Hospital
- To characterize the empiric antibiotic regimens used to treat patients with suspected MRSA infection at Kelowna General Hospital

Study Design

Overview

This study will be a retrospective chart review and will assess the susceptibility patterns and empiric antibiotic therapy for MRSA infections at Kelowna General Hospital from June 1, 2008 to May 31, 2009. The investigators for this study, who are responsible for designing the study and developing the study methodology, include a Doctor of Pharmacy Student, Clinical Pharmacy Specialist in Emergency Medicine, a Clinical Pharmacy Specialist in Infectious Diseases and a Medical Microbiologist. A University of British Columbia undergraduate pharmacy student will be responsible for collecting the study data.

Patient Selection

Patients will be considered for inclusion into this study if they had a positive culture for a suspected infection or a positive screening culture for MRSA obtained at Kelowna General Hospital between June 1, 2008 and May 31, 2009.

Inclusion Criteria

- Males and females 18 years of age or older

Exclusion Criteria

- Males and females less than 18 years of age

Outcome Measures

The primary outcome of this study is the percentage of MRSA cultures resistant to different antibiotics, including clindamycin, sulfamethoxazole-trimethoprim, ciprofloxacin, moxifloxacin, tetracycline, erythromycin, linezolid or vancomycin. The secondary outcomes include the incidence of each type of MRSA infection, the incidence of identified MRSA risk factors and the percent of each empiric antibiotic chosen in this patient population.

Study Procedures

A list containing patient names, medical record numbers, patient ages, date(s) of MRSA culture and location of culture will be obtained from the microbiology laboratory database for all patients with a positive MRSA culture between June 1, 2008 and May 31 2009. Upon review of the obtained list, patients meeting the exclusion criteria will be excluded from the study. Patients meeting the study inclusion criteria will be included in the study. The hospital charts of included patients will be obtained from health records and will be reviewed to obtain patient demographic, clinical and social history information for the hospital visit in which the positive MRSA culture was obtained. In addition, the microbiology laboratory computer system will be accessed to obtain resistance patterns for each MRSA culture. The data collection form that will be used to collect the data is provided in Appendix I. Once all data is collected, it will be entered into a Microsoft Excel spreadsheet for analysis.

The following information, if available, will be obtained from each patient chart:

- Patient medical record number
- Patient demographic data
    - Date of admission or visit to hospital
    - Gender
    - Age
    - Location in hospital at time of culture
        - Emergency department
        - Hospital ward

        - Intensive care unit
- Patient clinical data and social history
    - Comorbid diseases
    - Any risk factors for MRSA (2)
        - Aboriginal
        - Athlete involved in a contact sport
        - Injection drug user
        - Homelessness
        - Recent hospitalization in the past year
            - In Interior Health Authority
            - In British Columbia
            - In Canada
            - Outside of Canada
        - Immunocompromised
        - Undergoing hemodialysis
        - Recent trauma in the past year
        - Indwelling catheter in time of culture
        - Percutaneous device at the time of culture
    - Site of infection
    - Name(s) of empiric antibiotic(s)

The following information, if available, will be obtained from the Microbiology Laboratory computer system:

- Date of MRSA culture
- Site(s) of MRSA culture
- Whether the organism was sensitive, intermediately sensitive or resistant to
    - Clindamycin
    - Sulfamethoxazole-trimethoprim
    - Ciprofloxacin
    - Moxifloxacin

- Tetracycline
- Erythromycin
- Linezolid

- Vancomycin Minimum Inhibitory Concentration (MIC)
  - <0.5
  - 0.5-1.0
  - 1.1-1.5
  - 1.6-2.0
  - >2

Evaluation of Study Outcomes and Statistical Analysis

All data obtained from the patient charts and the Microbiology Laboratory system will be entered into a Microsoft Excel Spreadsheet for analysis. Microsoft excel will be used to determine the number and percent of MRSA cultures resistant to the pre-specified antibiotics and to categorize and calculate the number and percent of MRSA infection type, risk factors for MRSA infection and type of empiric antibiotic therapy given. Descriptive statistics, specifically the mean, standard deviation and percent will be used when analyzing the patient demographic, clinical and microbiologic characteristics.

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Appendix I: **Study Data Collection Form**

Patient Name: Patient ID: Age:

Gender: Weight (kg): Date of Admission/Visit:

Location in Hospital in Time of Culture

__EMERG __Ward __ICU

Type of Culture

__Screen __Culture for Infection __Both

Comorbid Diseases (check all that apply)

__COPD __Diabetes __Rheumatoid Arthritis __Osteoarthritis __Heart Failure

__Asthma __Hypertension __Other_____

MRSA Risk Factors (check all that are present)

__Athlete

__IVDU

__Aboriginal

__Homeless

__Immunocompromised

__Hemodialysis

__Trauma in last year

__Indwelling catheter (at time of culture)

__Percutaneous device (at time of culture)

__Hospitalization in last year

__In Interior Health

__In BC

__In Canada

__Outside Canada

__Not available

Susceptibility to Antibiotics (S,I,R)

__Clinda __Septra __Cipro

__Levo __Moxi __Tetra

__Erythro __Linezolid

__Vancomycin MIC

__<0.5 __0.6-1.0

__1.1-1.5 __1.6-2

__>2 __Not available

Site(s) of Infection

__Skin and Soft Tissue __Diabetic Foot

__Skin Abscess __Pneumonia

__Buttocks Abscess __Bacteremia

__Surgical Wound __Urinary Tract

__Traumatic Wound __CNS

__Bone/Joint/Hardware __Other_____

Date of Culture_____

Site(s) of Culture

__Blood __Sputum __Urine

__Bronchoscopy __Wound __CSF

__Nasal swab __Rectal Swab __Other_____

Incision/Drainage Performed

__Yes __No

Empiric Antibiotics

__Yes __No

Empiric Antibiotics

__Cefazolin __Cefazolin and probenicid

__Clinda iv __Clinda po

__Cipro __Moxi

__Clox iv __clox po

__cephalexin __amoxicillin/clavulanate

__doxycycline __vancomycin

__linezolid __Septra __Other_____

Is culture susceptible to empiric antibiotic choice?

__Yes __No __Not Available __Empiric Abx not tested