Effect of Antibiotics on Community-Associated Staphylococcus aureus Colonization and Recurrent Infection in Patients with Uncomplicated S. aureus Skin Abscesses

PI: Marcela Rodriguez, MD
Sub-I's: Myto Duong, MB, BCh, BAO, MS
Stephanie Fritz, MD

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SIGNIFICANCE

CA-*S. aureus* burden

Community-associated *S. aureus* infections have become a significant public health problem throughout the United States. These infections span a wide range in severity from superficial skin abscesses to invasive pyomyositis, severe necrotizing pneumonia and fatal septicemia [7-11]. Recurrent *S. aureus* SSTI are problematic and recurrence rates have been reported in up to 50% of pediatric patients [12-16]. Recurrent *S. aureus* infections requiring emergency center care is common and accounts for significant utilization of hospital resources [17]. The incidence of *S. aureus* SSTI has risen dramatically over the past decade [18], such that cellulitis and soft tissue abscesses are the most frequent primary diagnoses associated with *S. aureus.* In 2005, there were 14.2 million outpatient clinic visits for SSTI (48.1 visits/1000 in the US) compared with just 8.6 million visits (32.1 visits/1000) in 1997 [18]. Due to this substantial burden, MRSA is a top priority for the Institute of Medicine's Comparative Effectiveness Research Program [19]. The annual economic burden of MRSA infection in the United States is approximately $14 billion [20]. At SJH and MMC in Springfield, Illinois, we have seen a significant increase in the number of pediatric ED and EC visits. In the last five years there has been an average of 1400 visits a year for SSTI, which counts for more than a fifty percent increase during this time period.

Determinants of CA-*S. aureus* infections

Traditionally, *S. aureus* skin colonization occurs most frequently in the anterior nares, but it can also colonize the axilla, inguinal fold, rectum, and throat [5, 21]. *S. aureus* nasal colonization is a risk factor for SSTI development [22-25]. Multiple sites of *S. aureus* colonization have been found to be related to higher recurrence rates [26]. Increased rates of SSTI have been described among U.S. military personnel colonized with CA-MRSA; soldiers with CA-MRSA nasal colonization had a 10-fold greater risk of developing SSTI than soldiers colonized with Methicillin susceptible *S. aureus* (MSSA) [23]. Endogenous colonization is important in the transmission and pathogenesis of CA-MRSA infection but behavioral and environmental factors may be equally important [27].

Management of CA-*S. aureus* abscesses

It is controversial whether abscesses requiring incision and drainage also require antibiotics [28]. The frequency of antibiotic prescription in *S. aureus* SSTI is still common as described in the literature [29]. Creech et al surveyed over 100 Pediatric Infectious Diseases Consultants and found that all of them (N=197) prescribed antibiotics; no provider reported using incision and drainage alone without antibiotic therapy [30]. Mc Neil et al reported an almost 95% rate of antibiotic prescription among children with *S. aureus* SSTI at Texas Children's Hospital [31].

In a study done by Ruhe et al, patients with SSTIs caused by MRSA benefited from antibiotic treatment. Patients with CA-MRSA SSTI who received antibiotics in addition to incision and drainage had a greater treatment success rate (infection cure) than those managed with incision and drainage alone (95% versus 87%, P =.001) [32]. In a randomized trial by Duong et al, treatment failure rates for CA-MRSA skin abscesses were similar after incision and drainage between patients who received antibiotics and those given a placebo. However, at 10-day follow-up, new lesions formed in 26.4% of cases in the placebo group and only 12.9% of cases in the antibiotic group [12]. Schmitz et al showed a similar incidence of treatment failure in adult patients with uncomplicated abscesses receiving trimethoprim-sulfamethoxazole versus placebo (17% vs 26%, P=.12); but at 30-day follow-up the incidence of new lesions was lower in the antibiotic group compared to the placebo group (9% vs 28%, P=.02) [33].

Significance for our community

Recurrent *S. aureus* SSTI have become a major source of morbidity in our pediatric population. Like other areas of the United States, our community has seen a dramatic increase in the incidence of skin and

soft tissue infections among previously healthy children. At SJH the number of pediatric ED visits related to SSTI increased more than fifty percent in the last 5 years, from 160 visits a year from 2008-2009 to 360 visits a year from 2013- 2014. While many of these infections are superficial, they provoke pain and anxiety for children and families, lead to subsequent scarring, and pose a significant burden through lost time from school and work. Decreasing the number of recurrent SSTI will decrease ED, EC and PCP clinic visits and will benefit our community health in general.

INNOVATION

Infections due to *S. aureus* are a major healthcare burden. Currently there is not an effective way to prevent *S. aureus* infection. Antibiotics are often prescribed for the treatment of CA-*S. aureus* SSTI. While incision and drainage alone may be adequate for management of uncomplicated CA-*S. aureus* skin abscesses, there is uncertainty about the requirement of systemic antibiotics. It is not known whether antibiotics are helpful in decreasing *S. aureus* colonization rates or preventing future *S. aureus* infections. Though resolution of acute abscess after drainage may be unchanged by antibiotic administration, the impact of managing *S. aureus* abscess without antibiotics on ongoing *S. aureus* colonization and recurrent infection requires further study. This study seeks to examine whether the management of initial *S. aureus* abscesses with incision and drainage in addition to antibiotic therapy is an effective means of preventing recurrent infection. The prolonged longitudinal follow-up of this study is a unique characteristic that will enable us to capture data about recurrences of infections.

APPROACH/PRELIMINARY DATA

Risk factors for *S. aureus* SSTI

MRSA colonization confers risk for SSTI: A prevalence study of *S. aureus* nasal colonization in the St. Louis pediatric population was performed by Fritz et al.; 1300 children ages birth to 18 years were enrolled. The rates of MRSA and MSSA nasal colonization were 2.5% and 25.5%, respectively [10]. To investigate the relationship between *S. aureus* nasal colonization and subsequent SSTI, the 1300 children enrolled in the above prevalence study were followed for one year, during which the overall incidence of SSTI was 13%. Baseline MRSA colonization conferred risk for subsequent SSTI (OR 4.6, 95% CI 1.8, 11.9) [10]. Another study performed by Kaplan et al showed that multiple *S. aureus* colonization sites were related with higher recurrence rates [26].

Household member with SSTI: S. aureus SSTI cluster in households. In a study performed by Fritz et al, SSTI in a household contact was associated with increased risk of SSTI in the index patient (**Figure 1**) [22].

Figure 1
Significant Risk Factors for Development of SSTI during a 12- Month Longitudinal Study, Univariate Analysis

Risk Factor	OR	95% CI
MRSA nasal colonization	4.6	1.8 – 11.9
Skin infection in year prior to enrollment	4.2	1.8 – 9.7
Household member with skin infection in year prior to enrollment	2.9	1.2 – 6.8
Interval skin infection in a household member during one-year follow up	6.4	3.4 – 12.2
African-American race	3.1	1.5 – 6.4
Crowded home (>2 people/bedroom)	4.4	1.1 – 18.2

Colonization pressure is a Risk Factor for subsequent SSTI: Colonization pressure (CP) is a measure used in healthcare settings to determine the magnitude of the microorganism reservoir. MRSA CP has been shown to predict infections in hospitals [34]. During my fellowship at Washington University under the mentorship of Stephanie Fritz, MD, MSCI, I participated in a study aimed to apply the concept of CP to the community setting by evaluating whether the proportion of colonized household contacts increased the prevalence of persistent colonization or the incidence of recurrent infections in index patients with baseline SSTI. We demonstrated that high MRSA CP in households was associated with persistent MRSA colonization in pediatric patients. We found a relationship between *S. aureus* household CP and a history of SSTI in household contacts in the year prior [35].

Effect of Antibiotics on CA-MRSA colonization and recurrent infection in uncomplicated skin abscesses

From 2008-2010, 852 adults and children with MRSA skin abscesses were enrolled at St. Louis Children's and Barnes-Jewish Hospitals. MRSA colonization status was determined at baseline and repeated 2-8 weeks later (for 194 patients). Of the 147 patients with MRSA colonization at screening who provided a follow-up culture, those prescribed an antibiotic for MRSA were less likely to be MRSA colonized at follow-up than those who were not prescribed an antibiotic (39% vs 100%, p=0.01). The likelihood of MRSA colonization also varied depending on which antibiotic was prescribed. Patients prescribed clindamycin were less likely to be MRSA colonized than those prescribed TMP-SMX (30% vs 54%, p=0.01). Patients prescribed an antibiotic active against MRSA were less likely to have a recurrent SSTI over the subsequent year than patients who were not prescribed an antibiotic (aOR=0.32, 95% CI 0.12, 0.90) [36].

Experimental Design and Methods

Patient recruitment**:** This is a prospective case-control study that will be performed by the SIU Division of Pediatric Infectious Diseases in collaboration with SJH ED, MMC ED, SIU General Pediatrics Clinics and the Division of Pediatric Infectious Diseases at Washington University School of Medicine. Children who present to SJH or MMC through the ED or SIU Pediatrics clinics with a skin abscess (first episode or recurrent) will be assessed for study eligibility. Cases are defined as patients with a *S. aureus* skin abscess who had incision and drainage AND had appropriate systemic antibiotic therapy. Controls are defined as patients with *S. aureus* skin abscesses who had incision and drainage and did NOT have systemic antibiotic therapy. This is a non-interventional study and treatment of skin abscesses will be at discretion of the treating physician. We expect to complete patient enrollment in six months with a six month follow-up period (see timeline, **Figure 2**). Members of the study team (Principal Investigator (PI), and Research Coordinator) will obtain access to SJH and MMC ED computerized patient tracking boards to monitor for potential candidates/participants. In addition we also plan to approach the SIU ED residents and attending physicians at MMC ED and the SIU Pediatrics Residents and Faculty from General Pediatrics Clinics to request notification when a potentially eligible patient is treated. We will also get access to the SIU Pediatrics clinic schedules to look for potential candidates. A copy of the approved protocol will be given to the attending physicians and residents so that they are aware of the study requirements. A member of the study team (PI or research coordinator) will then approach the patient and his or her parent or legal guardian to discuss his or her participation in this study.

Figure 2:
Timeline & Assessment Schedule

Activity	Site	Assessment	Project Months											
			1	2	3	4	5	6	7	8	9	10	11	12
Recruitment and enrollment	SJH-MMC-PCP clinics	Consent/Assent	■	■	■	■	■	■						
Colonization swabs at enrollment and collection of wound isolate	SJH-MMC-PCP clinics	Swabs x 3/ Wound isolate	■	■	■	■	■	■						
Follow up visit #1 (+1 month)	SIU Peds ID clinic	Swabs x 3		■	■	■	■	■						
Culture based analysis	WashU lab		■	■	■	■	■	■						
Follow up phone call (+3 months)	SIUSM	SSTI recurrence	■	■	■	■	■	■	■	■	■			
Follow up phone call (+6 months)	SIUSM	SSTI recurrence				■	■	■	■	■	■	■	■	■
Follow up phone call (+12 months)	SIUSM	SSTI recurrence						■	■	■	■	■	■	■
Data analysis	SIUSM								■	■	■	■	■	■

Inclusion criteria: (1) Children 6 months to 18 years presenting with a skin abscess. (2) Positive MRSA or MSSA culture from previous or current abscess

Exclusion criteria: (1) Immunodeficiency; (2) Hospitalization within the prior 14 days; (3) Use of mupirocin, clorhexidine or bleach water baths in the last month; (4) Systemic antibacterial therapy with anti-staphylococcal activity within the prior 14 days.

Assent will be obtained from children greater than 7 years of age. Informed consent will be obtained from the patient's parent or legal guardian. The study protocol was approved by the Southern Illinois University (SIU) Institutional Review Board (IRB). Risks for participating in the study are minimal; the only intervention that will be done is collection of body surfaces swabs.

Data Collection: At study enrollment, a detailed questionnaire will be administered to identify risk factors for *S. aureus* colonization, infection, and transmission. Clinical data will be collected as well to track clinical signs at the time of presentation (vital signs, body site of infection, size of abscess, presence of systemic symptoms, type of incision and drainage, antibiotic use, type of packing applied). In addition, colonization swabs from the nose, axilla, inguinal folds and wound isolate will be collected and transported to Dr. Stephanie Fritz's laboratory at Washington University. Longitudinal study visits will be conducted at the SIU Pediatric Infectious Disease Clinic one month following enrollment for research purposes only by PI or by the research coordinator. At this visit, a follow-up questionnaire will be administered inquiring about new, recurrent, or relapsed infection. Colonization swabs will be obtained and transported to Dr. Fritz's laboratory. Also history of any household members with any recent SSTI will be asked. Follow-up phone calls will be administered at 3, 6 and 12 months after enrollment to ask about recurrent infections. If an interval infection did occur, we will collect data regarding whether the individual sought medical care (and if so, the location where medical care was sought), the date of infection, the body site of infection, the bacteria causing infection, if known, whether the individual required a drainage procedure, surgery, or hospitalization, and whether the participant received antibiotics, oral or intravenous. If the patient sought medical care, records from the hospital and/or provider's office will be obtained for verification. Again, question about any household member having an SSTI will be made. Throughout the longitudinal study, we will ask participants to contact us if they develop a SSTI. The participant will be directed to seek medical treatment from their primary healthcare provider.

Microbiology: Colonization swabs will be obtained at enrollment and at the 1 month follow-up visit by the PI or the research coordinator from the nose, axilla and inguinal folds. Four swabs will be used for each participant (1 each for both nostrils, both axillae, and both sides of the groin and the abscess site). Specimens will be collected with Copan E-swab ™ Collection and Transport System to evaluate *S. aureus* colonization. This is a liquid-based multipurpose collection and transport system that maintains viability of aerobic, anaerobic and fastidious bacteria for 48 hours at room and refrigerator temperature. The research coordinator and I have successfully completed training for Shipping Infectious Materials and Biological Substances with SIU School of Medicine. Specimens will be shipped to Washington University in St. Louis, to the laboratory of Dr. Stephanie Fritz for microbiologic studies. If wound isolates from initial infection and a recurrence are available, they will be requested at the microbiology laboratory at SJH or MMC. After arrival, specimens will be incubated overnight in tryptic soy broth with 6.5% NaCl at 35°C. A sample of the broth will be plated to mannitol salt agar and incubated for 24-48 hours. Following confirmatory testing for *S. aureus* [37], susceptibility testing for cefoxitin (a surrogate for methicillin resistance) and 9 other antibiotics will be determined by Kirby-Bauer disk diffusion, in accordance with published guidelines [37]. Inducible clindamycin resistance will be tested [38]. All isolates will be stored in glycerol at -20ºC.

Sample size: This is a pilot study to determine the feasibility of recruiting patients as described, having them return for 1 follow-up visit, and collaborating with Washington University for future

investigations. Our goal is to get preliminary data. According to available billing records (ICD-9 codes), since 2010, there has been in average 130 pediatric visits per month at SJH, MMC ED and Express Cares secondary to SSTI. Our goal is to recruit 50 patients in 12 months, which means that we will need about a 30% success rate for recruitment (**Figure 3**). A sample size estimate was performed to evaluate the power in the study. Considering an incidence of recurrent SSTI of 50% in patients who did not receive antibiotic therapy, a 60-75% percent reduction of recurrent SSTI (12-20% incidence) can be shown with 50-80% power.

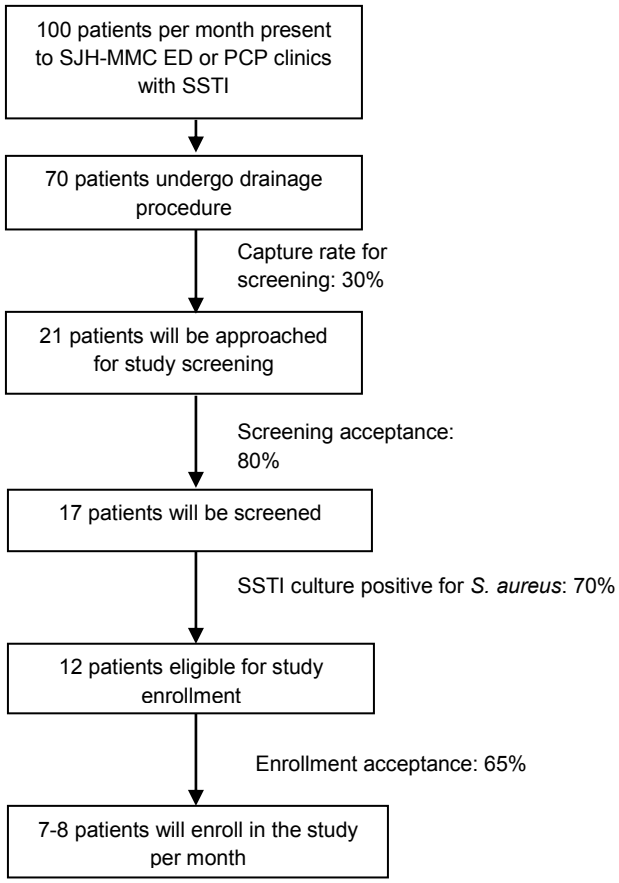
Data Analysis Plan

Data on *S. aureus* identification will be collected from Washington University School of Medicine and recorded, along with questionnaire and clinical variables, on a data collection form by the principal investigator and research coordinator and then transferred to an excel spreadsheet for statistical analysis. Statistical Package for the Social Sciences (SPSS), version 20, will be used for data analysis.

Descriptive Statistics will be computed for all study variables. Continuous variables will be described with measures of central tendency (mean, median) and dispersion (range, standard deviation). Categorical variables will be summarized as frequencies and percentages.

We will calculate the frequencies/ percentages for patient demographics, clinical characteristics, baseline questionnaire, follow-up questionnaires, and *S. aureus* colonization (nose, axilla, and inguinal folds) for each group: 1) Systemic antibiotic therapy 2) No systemic antibiotic therapy. Characteristics will be compared using independent t-tests for continuous variables and Chi-squared tests of independence for categorical variables. Significance will be assumed when $p < 0.05$ or the 95% confidence interval.

Figure 3: Monthly Study Accrual Rates



Specific Aim 1:

Primary outcome:

To determine *overall* colonization status in children presenting with *S. aureus* abscesses who do and do not receive systemic antibiotic therapy at two time points (baseline and 1 month); a hierarchical logistic regression model will be used with colonization status as the outcome. Follow-up tests will be utilized when necessary.

Secondary outcomes:

1. To determine colonization status *at each body site* (nose, axilla and inguinal folds) independently in children presenting with *S. aureus* abscesses who do and do not receive systemic antibiotic therapy at two time points (baseline and 1 month); a hierarchical logistic regression model will be used with colonization status as the outcome at each body site.
2. A chi-squared test of independence will be used to determine if there is an association between colonization (determined at baseline) and presence of abscess at 1 month.

Specific Aim 2:

Primary outcome:

To measure incidence of SA recurrent skin and soft tissue infections at 3 months in patients who did or did not receive systemic antibiotic therapy. A binary logistic regression will be performed to see if antibiotic therapy is associated with SSTI at 3 months after adjusting for covariates.

Secondary outcomes:

1. To measure incidence of SA recurrent skin and soft tissue infections at 1, 6 and 12 months independently in patients who did and did not receive systemic antibiotic therapy. Separate logistic regressions will be performed (at each time point) to see if antibiotic therapy is associated with SSTI after adjusting for covariates.
2. In order to assess the trend of SSTI's over 1 year follow-up we will use the Cochran-Armitage test for trend to determine if there are more SSTI's in the following year for patients colonized (determined at baseline).

Specific Aim 3:

Primary outcome:

To measure *S. aureus* antibiotic resistance in patients who did and did not receive systemic antibiotics, we will use a chi-squared test of independence to compare antibiotic resistance between patients who did and did not receive antibiotic therapy.

Potential limitations:

Recruitment success rate is estimated to be around 30% in order to collect the desired patient sample (50 patients) in a 1 year period; this is based on a prior study in which the same population was targeted [39]. We recognize the complexity of having patients come to clinic for research purposes only in follow up. SIU School of Medicine's Department of Pediatrics is providing funds to complete the study beyond the 12 month period. Patient reimbursement of a $20 check will be given at the follow-up visit for study purposes, without any charges to medical insurance. In previous studies conducted by our team, we had had a high longitudinal retention rate when the same incentive was given [39, 40]. Specimens will be obtained by research personnel and the collection technique. The surface area swabbed and the pressure used will be standardized for all participants. We have validated the shipping procedures for specimen transport to our collaborators at Washington University. We would like to evaluate whether shipment of the swabs can be done in a timely manner and whether the length of time required for shipment impacts the ability to successfully recover microorganisms. Reaching participant for follow-up phone calls may be a challenge, especially at 6 and 12 months after study enrollment; thus, we will obtain multiple methods of contact for each participant. A source of bias that we will have is the variability in the treating physician's decision to administer antibiotics or not. Adjusting for possible confounding factors and covariates will be made but these factors will not play a role in the primary outcome which is *S. aureus* colonization.

Conclusion: The Research Seed Grant, RSG, is an important step in achieving my career goal of becoming an independent investigator at SIU and will offer me a tremendous opportunity to help our patient population. The goal of this project is to obtain preliminary data which will allow me to apply for future external funding to be able to recruit more patients and to show a statistical significance. Recurrent *S. aureus* SSTI have become a major source of morbidity in our pediatric population. Decreasing the number of recurrent SSTI will decrease ED and PCP clinic visits and will benefit our public health.