An Investigation of Antibiotic Susceptibility to Empiric Therapy for Community-associated Methicillin-resistant *Staphylococcus aureus*

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ABSTRACT

Objective: To analyze antibiotic susceptibility patterns of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) isolates obtained from skin and soft tissue infections among Wisconsin outpatients.

Design: Retrospective genotype testing.

Setting: Isolates were forwarded to the Wisconsin State Laboratory of Hygiene and Marshfield Labs from clinical laboratories throughout Wisconsin.

Methods: MRSA isolates submitted during April, 2010–February, 2012 underwent genotype analysis using pulsed-field gel electrophoresis. Antibiotic susceptibility patterns were determined for all isolates identified by electrophoresis subtyping as strain type USA300, and pattern comparisons were made by public health region.

Results: Among 835 MRSA isolates submitted, 217 (26%) were genotyped. Of these, 152 (70%) were USA300 MRSA. Among the 152 USA300 isolates, 95% were susceptible to clindamycin and 99% were susceptible to tetracycline and trimethoprim-sulfamethoxazole. The proportion of clindamycin-susceptible isolates from the southern region was significantly lower when compared to the other 4 regions combined ($P = 0.03$). One southern region clindamycin-resistant isolate was also resistant to trimethoprim-sulfamethoxazole.

Conclusions: USA300 MRSA was the predominant strain isolated from outpatient skin and soft tissue sites. Antibiotic susceptibility patterns among Wisconsin USA300 MRSA isolates are similar to patterns found in national studies. Local providers should continue to follow national practice guidelines for treatment of outpatient skin infections. A cluster of 4 clindamycin-resistant isolates and 1 trimethoprim-sulfamethoxazole resistant isolate was detected in the southern region, warranting continued surveillance for antibiotic resistance among community-associated MRSA isolates.

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INTRODUCTION

Staphylococcus aureus causes myriad of infections ranging from superficial skin and soft tissue infections to more invasive infections such as pneumonia, septicemia, and endocarditis.[1]

During the 1960s methicillin-resistant *S aureus* (MRSA) emerged among people with health care-associated risk factors. Health care-associated MRSA is typically resistant to all antibiotics except vancomycin and newer agents such as linezolid and daptomycin. These infections classically occur among older patients, recently hospitalized patients, nursing home residents and people exposed to invasive devices or procedures. Health care-associated MRSA is commonly associated with serious invasive infections such as pneumonia and bacteremia.[1,2]

Community-associated MRSA emerged during the 1990s among people with no health care-associated risk factors. This strain of MRSA typically is resistant only to the beta-lactam antibiotics and is most commonly associated with superficial skin and soft tissue infections.[1] Community-associated MRSA infections of the skin tend to be more purulent in nature compared to beta-hemolytic streptococcal infections, which generally lack purulence and exudates.[3] Community-associated MRSA infections usually occur among younger individuals compared to persons typically infected with health care-associated MRSA.

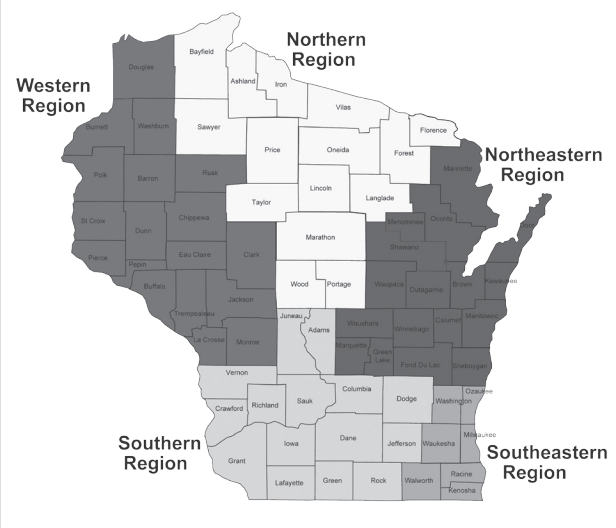
Evidence-based recommendations to guide antibiotic treatment of community-associated MRSA infections were lacking until recently. In 2011 the Infectious Disease Society of America published evidence-based clinical practice guidelines for

Table 1. Empiric Oral Antibiotic Treatment of Purulent SSTIs[3]

Treatment	Adult Dose	Strength of Recommendation
Clindamycin	300-450mg TID	A-II
TMP-SMX	1-2 DS tab BID	A-II
Doxycycline	100mg BID	A-II
Minocycline	200mg x1, then 100mg BID	A-II
Linezolid	600mg BID	A-II

Abbreviations = SSTIs, skin and soft tissue infections; TID, three times daily; BID, twice daily; DS, double strength; TMP-SMX= Trimethoprim-Sulfamethoxazole.

Figure 1. Wisconsin Division of Public Health Regions



treatment of a variety of MRSA infections. Incision and drainage continues to be the recommended primary treatment in simple boils and abscesses.[3] In settings where incision and drainage alone are not adequate such as severe or extensive disease, patient comorbidities, or failed incision and drainage, the recommendations include first line oral antibiotic options for empiric coverage of community-associated MRSA among outpatients with superficial skin infections.

The Centers for Disease Control and Prevention reports strain type USA300 MRSA as the predominantly circulating community strain in the United States. This strain is the major cause of skin and soft tissue infections in community settings such as daycare centers and correctional facilities.[1,4] USA300 MRSA is considered susceptible to all of the first-line oral antibiotic empiric therapies outlined in the 2011 evidence-based practice guidelines. Table 1 includes a brief summary of these empiric antibiotics for purulent lesions. Clindamycin is among the first-line options for empiric coverage, but the national guideline authors acknowledge that clindamycin susceptibility may vary by region.[3] Subsequently, the Wisconsin Division of Public Health initiated a statewide study to determine the proportion of USA300 MRSA isolates from skin infections that were susceptible to the empiric therapies outlined in these 2011 national practice guidelines. The results of that study are included in this report.

METHODS

We conducted a retrospective study of 217 MRSA isolates examined at 2 laboratory facilities in Wisconsin. The specimens were collected from superficial infections of skin and soft tissue among outpatients during April, 2010–February, 2012. Isolates were either referred to the Wisconsin State Laboratory of Hygiene (state lab) from clinical laboratories for confirmatory testing or were recovered from clinical samples submitted to Marshfield Labs. The isolates were obtained from patients in all 5 state public health regions (Figure 1).

All 99 outpatient MRSA isolates submitted to the state lab from the northeastern, southeastern and southern regions underwent genotype analysis using pulsed field gel electrophoresis. Among 736 outpatient MRSA isolates submitted to Marshfield Labs from the western, northern, northeastern and southern regions, 118 (16%) randomly selected isolates underwent electrophoresis genotype analysis. The number of genotyped isolates among each public health region ranged from 27 to 37.

Preparation of chromosomal DNA for electrophoresis analysis was performed using previously described methods[5,6] with slight modifications. Agarose plugs were made by mixing a standardized turbid bacterial suspension, molten agarose and lysostaphin. Cells were lysed by incubating plugs in Staphylococcus Lysis Buffer at 54°C for 2 hours (state lab) or in EC buffer at 37°C for 4 hours (Marshfield Labs). Lysis buffer was removed by washing twice in Millipore water and 4 times in TE Buffer. Plugs were restricted with 30 units of SmaI enzyme (New England Bio Labs, Inc, Ipswich, Massachusetts) for 2 hours at 25°C. DNA fragments were resolved in 1.0% agarose at 14°C for 18 hours (state lab) or 20 hours (Marshfield Labs). Switch times of 5.0 to 40.0 seconds and voltage of 6.0v/cm were applied using a CHEF Mapper XA Chiller System (Bio-Rad, Life Science Research, Hercules, California). Methods were validated by both laboratories using USA-series reference strains including USA300-0114 to assure inter-laboratory reproducibility. Analysis was performed using BioNumerics software (Applied Maths, Austin, Texas) with the Dice coefficient at 1.25% tolerance and the unweighted pair group of arithmetic averages algorithm. Genetic similarity was interpreted according to the criteria of Tenover et al.[7]

Antibiotic susceptibility testing was conducted on all MRSA isolates identified as USA300 MRSA. Susceptibility testing at Marshfield Labs was performed using the Phoenix System (BD Diagnostic Systems, Sparks, Maryland) PMIC panels according to the Clinical and Laboratory Standards Institute guidelines.[8]

Susceptibility testing at state lab was performed using a Kirby Bauer disk diffusion and the D Zone test, also according to the same established guidelines.[8] Antibiotic agents tested included erythromycin, clindamycin, levofloxacin, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin.

The proportion of USA300 MRSA isolates susceptible to selected antibiotic agents was determined statewide. Additionally, the proportion of isolates susceptible to clindamycin, trimethoprim-sulfamethoxazole, and tetracycline was determined by public health region and statistically significant differences among regional antibiotic susceptibility patterns were determined using the Fisher's exact test.

Table 2. Proportion of strain type (ST) USA300 MRSA Isolates Susceptible to Select Antibiotic Agents, by Wisconsin Public Health Region, April 2010–February 2012

Public Health Region	Western	Northern	Northeastern	Southeastern	Southern
Number of specimens	27	29	29	37	30
Clindamycin % susceptible	96	96	96	100	87
95% CI	(81–99)	(82–99)	(81–99)	(90–100)	(69–96)
P-value[a]	1.00	1.00	1.00	0.20	0.03[b]
TMP-SMX % susceptible	100	100	100	100	97
95% CI	(87–100)	(88–100)	(88–100)	(90–100)	(83–99)
P-value[a]	1.00	1.00	1.00	1.00	0.20
Tetracycline % susceptible	100	100	100	100	97
95% CI	(87–100)	(88–100)	(88–100)	(90–100)	(83–99)
P-value[a]	1.00	1.00	1.00	1.00	0.20

[a]*P*-value is for Fisher's exact test comparing the proportion of susceptible isolates in a single region to the proportion of susceptible isolates in the remaining 4 regions.
[b]statistically significant
Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole

Table 3. Proportion of Susceptible Wisconsin strain type (ST) USA300 MRSA Isolates Compared to EMERGEncy ID NET Isolates, by Antibiotic Agent

Agent	2010–2012 Wisconsin Number Susceptible/ Number Tested (% Susceptible) Isolates	2008 EMERGEncy ID Net[12] Number Susceptible/Number Tested (% Susceptible) Isolates	2004 EMERGEncy ID Net[2] Number Susceptible/Number Tested (% Susceptible) Isolates
Clindamycin	145/152 (95%)	344/366 (94%)	215/226 (95%)
Erythromycin	8/151 (5%)	34/350 (10%)	13/226 (6%)
Fluoroquinolones	50/82 (61%)	155/346 (45%)	111/176 (63%)
TMP/SMX	150/151 (99%)	366/367 (99%)	217/217 (100%)
Tetracycline	146/147 (99%)	343/350 (98%)	207/226 (92%)
Rifampin	151/151 (100%)	323/326 (99%)	186/186 (100%)
Vancomycin	151/151 (100%)	326/326 (100%)	No data

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole

RESULTS

Among 217 outpatient MRSA isolates tested, 152 (70%) were identified as USA300 and 4 (2%) were identified as USA400. These represent community-associated strains. The remaining 61 (28%) isolates were identified as USA100, USA500, and USA800, all of which represent health care-associated strains.[9] The age distribution of 165 patients with USA300 isolates was: age 0 - 4 years, 28; 5 - 17 years, 28; 18 - 44 years, 64; 45 - 64 years, 35; and ≥ 65 years, 10. The median age was 38 years. Among 103 patients for which information was available, 44% were males.

The proportion of USA300 isolates susceptible to selected antibiotic agents is provided by public health region in Table 2. The antibiotic susceptibility pattern was similar in all regions except for clindamycin susceptibility among southern region isolates when compared to isolates obtained from the remainder of the state (87% vs 98%, $P = 0.03$). The 4 southern region isolates that were nonsusceptible to clindamycin were obtained from 4 unique patients treated at 2 different outpatient clinics in the region. One of the 4 isolates, cultured from an eye specimen, is also the only isolate that was nonsusceptible to trimethoprim-sulfamethoxazole.

The overall statewide USA300 antibiotic susceptibility pattern is provided in Table 3, along with findings from national studies conducted among emergency department patients during 2004 and 2008. Among the antibiotics used for empiric treatment of community-associated MRSA, virtually no differences were noted between the Wisconsin and the national susceptibility.

DISCUSSION

The USA300 MRSA strain is becoming synonymous with community-associated staphylococcal disease in the United States. Outbreaks of community-associated MRSA infections among athletes, children attending daycare, and inmates of correctional facilities during the early 2000s demonstrate the dominance of a single electrophoresis pattern designated as strain type USA300-0114.[10,11] This strain continues to be a major cause of superficial skin infections among young healthy individuals.[11]

Two prospective prevalence studies were conducted during 2004 and 2008 among outpatients with acute, purulent skin infections seeking care at 1 of 11 EMERGEncy ID NET sites, a network of university-affiliated emergency departments in the United States. MRSA was isolated from 59% of approximately 1000 patients with superficial infections during the 2 studies, and USA300 comprised 97% of the MRSA isolates. USA300-0114 remained the dominant MRSA strain and its antibiotic susceptibility pattern was remarkably stable during 2004–2008.[12,13]

Table 4. Empiric Oral Antibiotic Treatment of Non-purulent SSTIs[3]

Treatment	Adult Dose	Strength of Recommendation
Beta-lactam (eg, cephalexin and dicloxacillin)	500mg QID	A-II
Clindamycin	300-450mg TID	A-II
Beta-lactam (eg, amoxicillin) and/or TMP-SMX	Amoxicillin: 500mg TID, TMP-SMX: 1-2 DS tab BID	
or a tetracycline	Doxycycline: 100mg BID	A-II
Linezolid	600mg BID	A-II

Abbreviations = SSTIs, skin and soft tissue infections; TID, three times daily; BID, twice daily; DS, Double Strength; TMP-SMX= Trimethoprim-Sulfamethoxazole; QID, four times daily.

The evidence-based practice guidelines for empiric treatment of skin and soft tissue infections released during 2011 were based heavily on the 2 aforementioned EMERGEncy ID NET studies and were founded on the premise that the majority of outpatient skin infections were caused by USA300 MRSA. Our findings in Wisconsin are similar to those of both national studies. Although USA300 MRSA isolates comprise a substantially smaller proportion of total MRSA isolates in Wisconsin compared to the EMERGEncy ID NET studies (70% vs 97%, $p < 0.01$), USA300 MRSA remains the predominant community-associated MRSA strain in Wisconsin and all isolates demonstrate the characteristic 0114 strain type pattern. Importantly, antibiotic susceptibility among Wisconsin USA300 isolates is remarkably similar to susceptibility patterns among USA300 isolates from the 2 national studies. In general, USA300 MRSA is considered susceptible to clindamycin, tetracycline, trimethoprim-sulfamethoxazole, rifampin, and vancomycin, with at least 90% of isolates susceptible to these antibiotics.

USA300 MRSA was resistant only to beta-lactam and macrolide antibiotic agents when initially isolated during 2000. During the past 5 years, clusters of clindamycin and tetracycline resistance among USA300 MRSA isolates have demonstrated broadening antibiotic resistance of this strain. Resistance is largely plasmid-mediated, highly transmissible and varies among patient populations.[14] For example, during a San Francisco General Hospital study, 16% of USA300 MRSA isolates among patients in a small outpatient HIV clinic were clindamycin resistant compared to 2% clindamycin resistance among a random sample of USA300 MRSA isolates obtained from the entire hospital-affiliated system.[3,15] Additionally, 48% clindamycin resistance was noted among USA300 isolates at the Fenway Community Health Center in Boston compared to only 7% clindamycin resistance among similar strains associated with a nearby health network.[16] Although overall susceptibility to clindamycin determined by national studies remains high, clusters of clindamycin resistance are evident. These clusters are acknowledged in the 2011empiric treatment guidelines, but clindamycin is still considered a first-line empiric therapy for USA300 MRSA skin infections, given the high levels of clindamycin susceptibility nationally.

Likewise, in our study of Wisconsin isolates clindamycin susceptibility was high (95%), but when stratified by public health region, a relatively high level of clindamycin resistance was observed in the southern region (13% vs 2% among the remaining 4 regions). In the context of the noted clusters, these regional differences in susceptibility among USA300 MRSA strains demonstrate the need for ongoing surveillance to more accurately describe variations in antibiotic susceptibility patterns among localities over time.

Beta-lactam antibiotic resistance among USA300 MRSA isolates is chromosomally encoded, but clindamycin resistance is mediated by the pSK41-like conjugative plasmid.[14] The pSK41-like plasmid previously was identified only in limited geographic areas such as the aforementioned San Francisco and Boston areas where clusters of clindamycin-resistant USA300 MRSA strains were detected. However, a 2010 analysis of national surveillance databases determined the pSK41 plasmid was present in 5 of the 8 states where surveillance was conducted. This plasmid is an important mechanism for the dissemination of clindamycin resistance among USA300 MRSA isolates. Prior to this 2010 study, it was believed the plasmid mediator for USA300 MRSA resistance was limited to a small number of rare clusters, but its proven presence in the surveillance database indicates the plasmid is more widespread than previously believed. This finding bolsters the case to continue monitoring community MRSA strains for emerging antibiotic resistance.[17]

Of note, 1 Wisconsin clindamycin-resistant USA300 MRSA isolate was also resistant to trimethoprim-sulfamethoxazole. Among approximately 1000 superficial infection samples enrolled in the EMERGEncy ID NET studies during 2004 and 2008, only 1 USA300 MRSA isolate was resistant to trimethoprim-sulfamethoxazole.[2,13] The mechanism conferring trimethoprim-sulfamethoxazole resistance in *S aureus* is linked to a gene carried on the same pSK41-like plasmid associated with clindamycin resistance, hence emergence of trimethoprim-sulfamethoxazole resistance via the same plasmid-mediated mechanism is of concern.

The authors of the 2011 practice guidelines recognized that treating outpatient skin infections with agents active against both community-associated MRSA and beta-hemolytic streptococci is controversial. Beyond clinical interpretations of purulent vs nonpurulent lesions as discussed previously, the need for broader coverage may depend on local epidemiologic features. Trimethoprim-sulfamethoxazole, doxycycline, and minocycline have demonstrated good in vitro activity against community-

associated MRSA, but their activity against beta-hemolytic streptococci is not well studied. Clindamycin is active against both community-associated MRSA and beta-hemolytic streptococci, but variable MRSA clindamycin susceptibility levels and emerging resistance must be considered when choosing an empiric treatment for outpatient skin infections, particularly among pediatric patients.[3] The 2011 Infectious Disease Society of America practice guideline recommendations for nonpurulent superficial skin infections are summarized in Table 4.

Our study has at least 3 noteworthy limitations. The retrospective design limited the availability of patient demographics, risk factors for MRSA acquisition, and clinical presentation (purulent vs nonpurulent lesions). Additionally, the number of isolates tested when stratified by region was small. Because clindamycin and trimethoprim-sulfamethoxazole resistance are relatively rare events, the small sample size may have reduced the ability to identify additional differences in regional antibiotic susceptibility patterns. Although the mechanism of resistance among Wisconsin clindamycin-resistant USA300 MRSA isolates is likely associated with the presence of the pSK41-like plasmid, this was not confirmed by laboratory analysis.

CONCLUSION

Consistent with national published data, USA300 MRSA is the predominately circulating MRSA strain associated with skin and soft tissue infections among Wisconsin outpatients. A small cluster of clindamycin-resistant isolates and 1 isolate determined to be resistant to both clindamycin and trimethoprim-sulfamethoxazole in 1 Wisconsin region demonstrate an antibiotic susceptibility pattern that is rare among community-associated MRSA isolates in national studies.

Overall resistance to non–beta-lactam antibiotics among Wisconsin USA300 MRSA isolates remains low and is comparable to findings in the national studies contributing to the 2011 practice guidelines. Local providers should continue to follow the 2011 practice guidelines released by the Infectious Disease Society of America for treatment of outpatient skin and soft tissue infections, but the emergence of resistance to these agents in at least 1 area of the state warrants further study. If history is a predictor, community-associated strains of MRSA will continue acquiring antibiotic resistance traits in its epidemic spread across the United States. Regional variation in antibiotic susceptibility must be monitored carefully through collaboration among private laboratory and public health partners.

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