Continued Decline in Community Acquired Invasive MRSA Infections at Texas Children's Hospital

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ABSTRACT

Background: The epidemiology of CA-*S. aureus* infections is changing with CA-methicillin susceptible *Staphylococcus aureus* (CA-MSSA) isolates causing an increasing share of both invasive and non-invasive SA infections at TCH. This study characterized this current epidemiology of invasive CA-MSSA infections.

Methods: The prospective CA-*S. aureus* surveillance database was queried for invasive SA infections between 2007 and 2014. CA-MSSA isolates were characterized using PFGE, spa typing *agr* and presence of *lukSF*-PV (*pvl*) genes. Medical records were reviewed. Statistical analyses included Fisher's exact and Wilcoxon test.

Results: CA-MRSA invasive infections decreased from 61 in 2007 to 20 in 2014 while CA-MSSA caused ~40-50 invasive infections annually and 66% of the invasive CA-*S. aureus* infections in 2014. (Figure) Similarly, CA-MRSA infections overall decreased from 1461 to 578 infections while CA-MSSA infections fluctuated between 400-650 infections, annually. We studied 296 (82%) of the invasive CA-MSSA infections with available isolates. Mean age was 8 years (range 0.01-18.3), 183 (62%) were male. Seventy-four (25%) isolates were USA300; 88 (30%) were *pvl*+. Bone and joint infections were most common (242, 82%) and associated with non-USA300 isolates (p=0.005); 74% were *pvl*-. In contrast, 8 of 12 pneumonia isolates were USA300 (p=0.001) and 11 (92%) were *pvl*+ (p<0.0001). Among patients with bone and joint infections, USA300 was associated with disseminated disease (13/52 vs 5/190, p<0.0001) and deep venous thrombosis [DVT] (11/52 vs 1/190, P<0.0001). Among a subset of 198 isolates, 75 spa types were identified; t008 (associated with USA300) represented 24% of isolates. Conclusion: Because of continuing decline in CA-MRSA for unknown reasons, CA-MSSA has been the most common cause of invasive CA-*S. aureus* infections at TCH since 2010. No single strain was a predominant cause of MSSA infections and the frequency of USA300 among the isolates has remained stable. CA-MSSA USA300 was associated with DVT, disseminated infection and pneumonia, similar to the clinical presentations among CA-MRSA. Our findings indicate niche specificity for USA300-*pvl* positive CA-MSSA isolates, similar to what has been observed among CA-MRSA.

OBJECTIVES

To present the current epidemiology of *S. aureus* infections at our institution with a focus on characterizing the invasive CA-MSSA infections and the associated isolates at our institution from 2007-2014.

INTRODUCTION

- *Staphylococcus aureus* USA300 emerged as the predominant cause of community acquired methicillin resistant *S. aureus* (CA- MRSA) infections nationwide in the early 2000's.
- The Center for Disease Control and Prevention reported an increase of invasive MRSA infections by 6.5% in 2013 and by 1.6% in 2014 compared to the previous year for all age groups. Sixty-eight % of the isolates were caused by USA300 in 2013 and 50% in 2014. (http://www.cdc.gov/abcs/index.html).
- At Texas Children's hospital (TCH), a surveillance study has been in place since August of 2001. We previously reported that >70% of all CA-*S. aureus* infections and nearly 60% of the invasive infections were caused by MRSA, >90% of which were USA300. We observed the USA300 genetic background among both MRSA and MSSA isolates.
- Panton-Valentine leukocidin (encoded by genes lukSF-PV; *pvl*) has been associated with the USA300 background and with severe disease presentations. Among invasive CA-MSSA, 12% of invasive non-USA300 CA-MSSA isolates carried *pvl* compared to 86% of invasive CA-MSSA USA300 isolates.
- We have become aware of a change in the distribution of CA-*S. aureus* infections TCH, primarily related to a decline in the number of infections caused by CA-MRSA. We hypothesized that changes in genetic distribution, with an increase of USA300 among invasive CA-MSSA isolates and an increase of *pvl* among diverse MSSA strain types would have occurred since our last investigation of invasive CA-MSSA from 2001-2006.

METHODS

Patients

- Patients were identified from a surveillance study at TCH. The study was approved by the Institutional Review Board at Baylor College of Medicine. Medical records review included demographics, primary diagnosis, underlying illness, and hospitalization

Isolates

- Clinical isolates were obtained from the Clinical Microbiology Laboratory at TCH.
- Antibiotic susceptibility patterns were determined (clindamycin, erythromycin, gentamicin, oxacillin, tetracycline, trimethoprim-sulfamethoxazole [TMP-SMX], vancomycin) by disk diffusion.
- Isolates were analyzed by pulsed field gel electrophoresis (PFGE) using standard techniques and by PCR for to determine the *agr* group and the presence of PVL genes (*lukS-PV* and *lukF-PV*). A subset of isolates underwent Spa-typing using the Ridom system (*spaserver.ridom.de).*

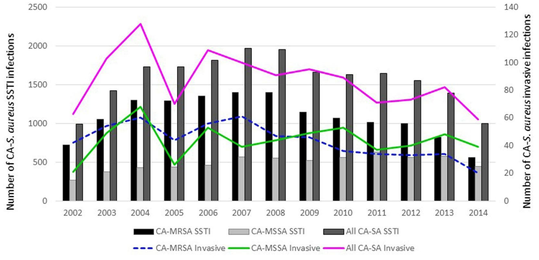
Statistical Analysis

- Fisher's exact test, Wilcoxon test and Chi-square for trend were performed using STATA 11 (College Station, TX). Analyses were 2-tailed, and a p<0.05 was considered statistically significant.

RESULTS

- Since the TCH surveillance study begun in August, 2001, the number of CA-MRSA infections initially increased, with a peak in 2007, and then subsequently decreased steadily as a cause of both CA-SSTI and invasive infections. (**Figure 1**).

Figure 1. Decrease of CA-MRSA as a cause of both SSTI and invasive infections.



- Among invasive CA-*S. aureus* infections, CA-MRSA decreased from 61 infections (28/10,000 admissions) in 2007 to only 19 (9/10,000 admissions) in 2014 (P<0.0007). (**Figure 2**). CA-MSSA infections fluctuated around 40-50 infections per year (18-24/10,000 admissions).
- CA-MRSA isolates were especially associated with pneumonia and deep seated abscesses, and CA-MSSA with bacteremia. (**Table 1**).
- CA-MSSA has been the most common cause of *S. aureus* bone and joint infections since 2008 and caused 73% of these infections in 2014.
- Clindamycin resistance was 13.5% among invasive CA-MSSA whereas CA-MRSA resistance rate was 7.7% (p=0.02).
- Patients with CA-MSSA were significantly older (p=0.0002).

Figure 2. Decrease of CA-MRSA as a cause of both SSTI and invasive infections.

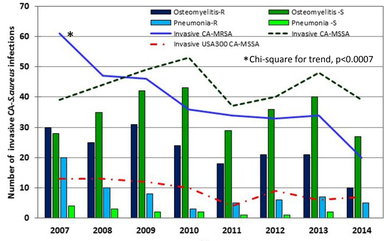
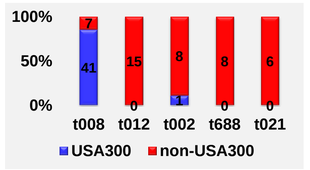


Table 1. Comparison of invasive CA-MRSA and CA-MSSA infections, 2007-2014

	CA-MSSA N=349	CA-MRSA N=311	P
Age median, range	8.0, 0.01-18.3	5.0, 0.02-17.4	0.0002
Gender male	220 (63.0%)	179 (57.6%)	0.2
Disease presentation			
Bone and joint	280 (80.2%)	180 (57.9%)	<0.0001
Bacteremia	20 (5.7%)	5 (1.6%)	0.007
Pneumonia	15 (4.3%)	64 (20.6%)	<0.0001
Deep seated abscess	13 (3.7%)	39 (12.5%)	<0.0001
Myositis/pyomyositis	11 (3.2%)	11 (3.5%)	0.8
Other	10 (2.9%)	12 (3.9%)	0.5
Antimicrobial non-susceptibility			
Clindamycin (n=658)	47 (13.5%)	24 (7.7%)	0.02
D test positive	36 (10.3%)	3 (1.0%)	<0.0001

*Data analysis of all database entries including patients without isolates available for study

Figure 3. Most common Ridom *spa* types.



- 296 invasive CA-MSSA isolates were available for study and included bone and joint infections (242, 82%), pneumonia/empyema (12, 4%), bacteremia only (13, 4%), myositis/pyomyositis (10, 3%), deep seated abscesses (9, 3%), and "other" (**Table 2**).
- African Americans were overrepresented among patients with USA300 isolates: 20/74 USA300 vs. 27/222 non-USA300 infections, p=0.005). Hispanics represented 90/222 non-USA300 vs. 16/74 USA300 infections, p=0.003)
- Selected data associated with each clinical presentation are presented in **Table 3**.
- Among 242 bone and joint infections, 145 were diagnosed with osteomyelitis alone, 25 with septic arthritis and 72 with both. Blood cultures were positive in 43% of patients overall but only in 20% of patients with septic arthritis. Almost 80% were non-USA300 and 74% were *pvl*-. Twelve patients had deep venous thrombosis and 14 presented with severe sepsis/septic shock. All 18 bone and joint patients with more complicated presentation (DVT, septic emboli, severe sepsis) had *pvl*+ isolates and 16 were USA300.
- All 12 patients with pneumonia presented with empyema, 10 were <1 year old. The majority of pneumonia isolates were USA300 (67%) and 92% were *pvl*+. Only 1 of 12 patients had a positive blood culture.
- Among the invasive CA-MSSA isolates 74 (25%) were USA300 and 29.7% were pvl+.
- All 4 *agr* groups were observed with different distribution for different disease presentations, with *agr* group 1 being the most common representing 57% of all isolates. (Table 3).
- USA300 decreased as a proportion of isolates from 34.5% in 2007 to 19% in 2014 (chi square for trend, p=0.008).
- A total of 75 known *spa* types were identified among 198 isolates, t008 represented 24% of the isolates. (**Figure 3**). Spa typing confirmed the diversity among isolates observed by PFGE, and the homogeneity of the USA300 isolates.

Table 2. Patient and isolate characteristics of invasive CA-MSSA infections, 2007-2014.[a]

	All N=296	USA300 N=74	Non-USA300 N=222	P
Age (median, range)	8.0, 0.01-18.3	6.8, 0.06-18.3	8.3, 0.14-17.9	0.3
Gender (male)	183 (61.8%)	41 (55.4%)	142 (64.0%)	0.2
Disease presentation				
Bone and joint	242 (81.8%)	52 (70.3%)	190 (85.6%)	0.005
Bacteremia	13 (4.4%)	1 (1.4%)	12 (5.4%)	0.2
Pneumonia	12 (4.1%)	8 (10.8%)	4 (1.8%)	0.002
Myositis/pyomyositis	10 (3.4%)	4 (5.4%)	6 (2.7%)	0.3
Deep seated abscess	9 (3.0%)	4 (5.4%)	5 (2.3%)	0.2
Other[b]	10 (3.0%)	5 (6.8 %)	5 (2.3%)	0.1
Antimicrobial non-susceptibility				
Clindamycin (n=295)	36 (12.2%)	4 (5.5%)	32 (14.4%)	0.06
D test positive	27 (12.4%)	0	27 (12.2%)	<0.0001
Erythromycin	96 (32.5%)	49 (67.1%)	47 (21.7%)	<0.0001
Gentamicin (n=204)	3 (1.5%)	2 (3.6%)	1 (0.7%)	0.2
TMP/SMX[c]	5 (1.7%)	0	5 (2.3%)	0.3
Tetracycline (n=254)	3 (1.2%)	0	3 (1.6%)	1
Molecular characteristics				
pvl+	88 (29.7%)	69 (93.2%)	19 (8.6%)	<0.0001
agr 1	170 (57.4%)	74 (100%)	98 (43.6%)	<0.0001
agr 2	51 (17.2%)	0	51 (23.0%)	<0.0001
agr 3	56 (18.9%)	0	56 (25.2%)	<0.0001
agr 4	10 (3.4%)	0	10 (4.5%)	0.07
Spa type t008 (n=198)	48 (24.2%)	41 (78.9%)	7 (4.8%)	<0.0001

[a]Patients with isolates available for study were included in the analysis, representing 82% of all identified CA-MSSA infections at Texas Children's hospital within the time period.
[b]Other diagnoses included 7 severe sepsis/septic shock/disseminated infection, 1 toxic shock syndrome, 1 peritonitis, 1 Stevens-Johnson syndrome with MSSA bacteremia
[c]TMP/SMX, trimethoprim-sulfamethoxazole

Table 3. Differences between invasive CA-MSSA clinical presentations, 2007-2014.

	Deep seated abscess N=9	Bacteremia N=13	Bone and joint N=242	Myositis/ Pyomyositis N=10	Pneumonia/ Empyema N=12	Other N=10	P
Age	3.5, 0.2-16.4	0.3, 0.01-13.7	8.7, 0.06-18.3	5.7, 0.07-14.0	0.73, 0.3-17.6	8.2, 0.6-14.9	
Hospitalized	9 (100%)	10 (76.9%)	241 (99.6%)	10 (100%)	12 (100%)	9 (88.9%)	ND
Hospital stay median days, range	10, 1-37	9, 5-18	8, 1-49	7, 3-25	12, 8-28	10.5, 4-21	ND
Positive BCx	2 (22.2%)	13 (100%)	105 (43.4%)	3 (30%)	1 (8.3%)	6 (60.0%)	<0.0001
median days, range	1, 1-2	1, 1-2	1, 1-8	1, 1	2	1, 1	ND
USA300	4 (44.4%)	1 (7.7)	52 (21.5%)	4 (40.0%)	8 (66.7%)	5 (50.0%)	0.001
pvl+	5 (55.6%)	0	62 (25.6%)	4 (40.0%)	11 (91.7%)	6 (60.0%)	<0.0001
agr group 1	5 (55.6%)	3 (23.1%)	142 (58.7%)	5 (50.0%)	10 (83.3%)	7 (70.0%)	0.06
agr group 2	2 (22.2%)	7 (53.9%)	41 (16.9%)	0	0	1 (10.0%)	0.008
agr group 3	2 (20%)	2 (15.4%)	47 (19.1%)	4 (40%)	1 (8.3%)	2 (22.2%)	0.6
agr group 4	0	1 (7.7%)	8 (3.3%)	0	1 (8.3%)	0	0.6
agr non-typeable	0	0	6 (2.4%)	1 (10%)	0	0	ND

CONCLUSIONS

- CA-*S. aureus* infections have decreased as a result of decreasing CA-MRSA, both among SSTI and invasive infections. For invasive MRSA infections, this may be due to an acquired immunity in the community to USA300.
- USA300 isolates also declined as a cause of CA-MSSA invasive infections further supporting the possibility of increasing immunity to USA300 clones, specifically.
- Both *pvl*+ and the USA300 genotype were associated with pneumonia and with bone and joint infections associated with DVT, septic emboli and/or severe sepsis, similar to previous findings among CA-MRSA infections.
- We did not find an increase of *pvl* among non-USA300 isolates.
- MSSA isolates now cause the majority of invasive *S. aureus* infections at our institution.
- The finding that USA300 and/or *pvl*+ cause similar disease presentations regardless of whether the strain is methicillin resistant or susceptible further establishes the virulence of this clone and suggests that *S. aureus* surveillance needs to include MSSA as well as MRSA infections.