Increasing Numbers of Staphylococcal Scalded Skin Syndrome Cases at Texas Children's Hospital are Caused by ST121

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ABSTRACT

Background: The molecular epidemiology of *S. aureus* strains causing staphylococcal scalded skin syndrome (SSSS) in the United States has not been described. We analyzed patient and *S. aureus* isolate characteristics associated with SSSS in children at Texas Children's Hospital (TCH) from 2008-2015.
Methods: Patients and *S. aureus* isolates were identified from an ongoing surveillance study. Patient chart review was performed. Patients with SSSS were identified by ICD9/10 codes through TCH Information Services. Molecular analysis included PCR for *agr, pvl, tst, eta*, and *etb*, pulsed-field gel electrophoresis (PFGE) and multi-locus sequence typing (MLST) to determine sequence type (ST).
Results: Cases of SSSS at TCH increased from 5 in 2008 to 58 in 2015 (Figure). For a majority of patients, no cultures were obtained or cultures were negative. Only 28 isolates were available, all MSSA, despite prospective collection. Cases were matched with 3 controls for age, MSSA and skin and soft tissue infection within the time period (Table). All available study cases were from 2013-2015. Twenty-nine percent reported positive rapid strep test and/or scarlatina (mainly prior to admission). Nikolsky's sign was noted in 50% of cases. Case and control isolates differed by all molecular markers (Table). Case isolates were mainly of CC121; one isolate lacked both *eta* and *etb* (ST5, *agr* II). One case isolate contained *pvl* and one *tst*; *etb* was uniquely found in cases but not in controls. Among the control isolates, 44% were USA300 and the majority were *pvl*+; two ST121 control isolates lacked both *eta* and *etb*. Clindamycin resistance was 15% for cases and 18% for controls.
Conclusion: Cases of SSSS are increasing at TCH; most have no cultures obtained or culture-negative specimens. *S. aureus* strains causing SSSS were likely to be of one clonal group, CC121 and carry *eta* and *etb*. We speculate that CC121 was recently introduced to our region and is responsible for the increasing numbers of SSSS cases that have been observed at TCH.

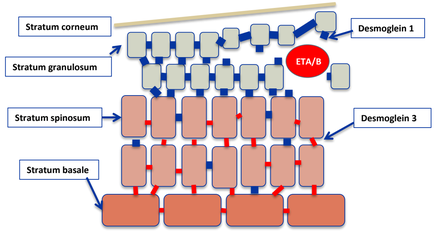
OBJECTIVES

- **To describe characteristics of SSSS within a pediatric population at Texas Children's Hospital (TCH) and compare the isolate characteristics to a control group matched by age and methicillin susceptibility.**

BACKGROUND

- Staphylococcal scalded skin syndrome (SSSS) is a generalized exfoliative skin infection that results in loss of superficial epidermis due to circulating toxins produced by *S. aureus*.
- Staphylococcal toxins *eta* and *etb* have been associated with the disease presentation. Their action is visualized in **Figure 1**.
- Studies outside of the United States have reported several clones associated with SSSS including ST 121.
- No contemporary data exist with regards to the molecular epidemiology of *S. aureus* strains causing SSSS in the United States.

Figure 1. Epidermal Exfoliation: Exotoxin (ETA and ETB) Target



METHODS

Study Design

- Patients with SSSS and their isolates were retrospectively identified from the *S. aureus* surveillance study database, from 2008-2015. Patients who were diagnosed as Ritter's Disease by ICD-9, or SSSS at the time of hospital discharge were included in the study.
- Isolates from age-matched patients with methicillin susceptible skin and soft tissue (SSTI) infections were identified from the study database within the same time period and included as controls at a 1:3 case-control ratio.

Patient Information

- Medical records were reviewed for demographic data, clinical presentation, treatment and laboratory values.

Laboratory Methods

- Antimicrobial susceptibilities were determined in the clinical microbiology laboratory.
- Molecular analysis was performed using PCR to detect *tst*, *pvl*, *eta* and *etb* and to determine the *agr* group.
- Pulsed field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) were used to determine strain relatedness. MLST allele and sequence type (ST) designation were obtained using the online MLST database (http://pubmlst.org/saureus/). SSSS clonal clusters (CC) were grouped amidst database isolates using eBURST (based upon related sequence types).

Statistical Analysis

- Cases and controls were compared using STATA11 (College Station, TX). Analyses included Fisher's exact and Wilcoxon rank-sum tests.

RESULTS

Cases

- The number of cases with ICD-9 coded Ritter's Disease or SSSS at the time of hospital discharge have increased annually since 2008, from 5 in 2008 to 57 in 2015. **Figure 2.**
- A majority of cases did not have cultures obtained as part of their work-up or the cultures were negative, with only a subset of patients having isolates available for analysis. Thus, only 28 patients with isolates available were included for study. All of the isolates were from 2013-2015. **Table 1.**
- 29% reported a positive rapid strep test and/or scarlatina; Nikolsky's sign was recorded as positive in 50% of the cases.

Case-Control

- No significant differences were observed in gender, ethnicity, age, or acquisition (community-acquired vs. community-onset healthcare associated vs. nosocomial) among SSSS or matched control patients. Antibiotic susceptibilities between the 28 SSSS strains and the 84 strains from the matched controls were similar.
- The SSSS isolates differed significantly from the control strains by *agr* group, toxin profile, and by PFGE and MLST. **Table 1.**
- The majority of the SSSS isolates were of the Clonal Complex 121 (CC121), *agr* group 4, *pvl*-, *tst*-, and carried *eta* and/or *etb*. None of the SSSS isolates were USA300 clone by PFGE; one was ST8. **Table 2, Figure 3.**
- Among the controls, 44.1% were USA300. 15/84 control isolates from different PFGE clusters underwent MLST including two control isolates that clustered with ST121 SSSS isolates by PFGE. These were ST121 by MLST and lacked *eta* and *etb*.

Figure 2. Patients with Ritter's Disease (ICD-9 code 695.81), 2008-2015

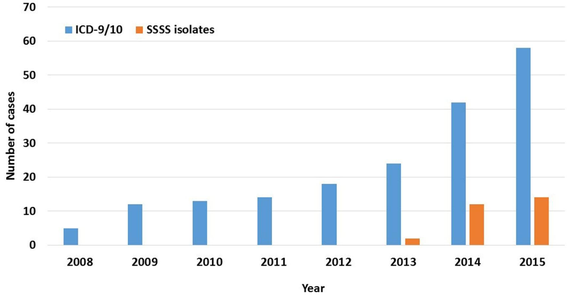


Table 1. Characteristics of SSSS cases and SSTI controls

Characteristic	Cases n=28	Controls n=84	P
Gender (male), n(%)	16 (57.1)	38 (45.2)	0.3
Race/Ethnicity, n(%)			0.06
Caucasian	15 (53.6)	20 (23.8)	
Hispanic	8 (28.6)	36 (42.9)	
African American	5 (17.9)	20 (23.8)	
Asian	0	4 (4.8)	
Other/Unknown	0	4 (4.8)	
Age (median, range)	0.9 (0.05-9.6)	1.1 (0.03-9.6)	0.2
Acquisition*			0.2
CA	27 (96.4)	69 (82.1)	
CO-HCA	1 (3.6)		
N	0		
Antimicrobial susceptibility			
oxacillin-S	28 (100)	84 (100)	ND
clindamycin-S	23 (82.1)	71 (84.5%)	0.8
Accessory gene regulator, *agr*			<0.0001
agr group 1	1 (3.6)	59 (70.2)	
agr group 2	1 (3.6)	5 (6.0)	
agr group 3	2 (7.1)	12 (14.3)	
agr group 4	24 (85.7)	3 (3.6)	
Non-typeable	0	5 (6.0)	
Panton-Valentine leukocidin, *pvl*+	1 (3.6)	52 (61.9)	<0.0001
Exfoliative toxin A, *eta*+	23 (82.1)	16 (19.0)	<0.0001
Exfoliative toxin B, *etb*+	27 (96.4)	0	<0.0001
Toxic shock syndrome toxin, *tst*+	1 (3.6%)	49 (58.3)	<0.0001
USA300	0	37 (44.1)	<0.0001

*CA, community acquired; CO-HCA, community onset healthcare associated; N, nosocomial

Figure 3. eBURST of SSSS Isolates together with the *S. aureus* MLST database Isolates

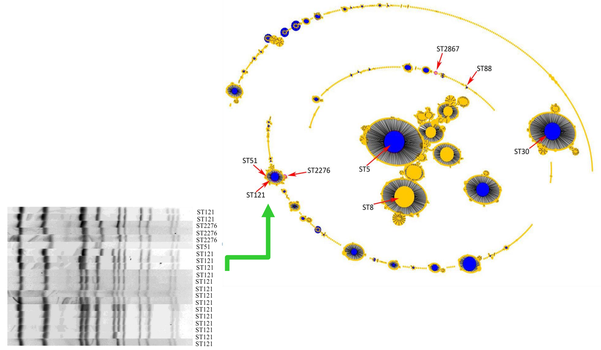


Table 2. Association between MLST and detection of virulence genes

ST	#of isolates	*agr* group 1	*agr* group 2	*agr* group 3	*agr* group 4	*pvl*+	*eta*+	*etb*+	*tst*+
5	1	0	1	0	0	0	0	0	0
8	1	1	0	0	0	1	1	1	0
30	1	0	0	1	0	0	1	1	1
51	1	0	0	0	1	0	0	1	0
88	1	0	0	1	0	0	0	1	0
121	20	0	0	0	20	0	19	20	0
2276	3	0	0	0	3	0	2	3	0

CONCLUSIONS

- **The number of patients with a primary diagnosis of SSSS has increased at TCH from 2008 to 2015; most have no cultures obtained or had culture-negative specimens.**
- **In this first study to detail the molecular characteristics of pediatric SSSS in the United States, we found all isolates to be MSSA, the majority to be clonally related and belonging to CC121. This finding is in contrast to other SSTI and invasive MSSA isolates among our patient population, where diverse genetic backgrounds have been described.**
- **No SSSS isolate had the common USA300 clone background, whereas USA300 represented 44% of the MSSA-SSTI control isolates.**
- **The current study findings are in agreement with contemporary studies outside of the US showing that SSSS isolates are likely to contain *eta* and *etb* and *agr* group 4.**
- **We speculate that CC121 was recently introduced to our region and is responsible for the increasing numbers of SSSS cases that have been observed at TCH.**
- **Further characterization of ST121, with regards to its genetic makeup and its role in other MSSA infections, is required to better understand its importance and the unique propensity of this strain to cause SSSS.**