Staphylococcal Toxic Shock Syndrome 2000–2006: Epidemiology, Clinical Features, and Molecular Characteristics

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Abstract

Introduction: Circulating strains of Staphylococcus aureus (SA) have changed in the last 30 years including the emergence of community-associated methicillin-resistant SA (MRSA). A report suggested staphylococcal toxic shock syndrome (TSS) was increasing over 2000–2003. The last population-based assessment of TSS was 1986.

Methods: Population-based active surveillance for TSS meeting the CDC definition using ICD-9 codes was conducted in the Minneapolis-St. Paul area (population 2,642,056) from 2000–2006. Medical records of potential cases were reviewed for case criteria, antimicrobial susceptibility, risk factors, and outcome. Superantigen PCR testing and PFGE were performed on available isolates from probable and confirmed cases.

Results: Of 7,491 hospitalizations that received one of the ICD-9 study codes, 61 TSS cases (33 menstrual, 28 non-menstrual) were identified. The average annual incidence per 100,000 of all, menstrual, and non-menstrual TSS was 0.52 (95% CI, 0.32–0.77), 0.69 (0.39–1.16), and 0.32 (0.12–0.67), respectively. Women 13–24 years had the highest incidence at 1.41 (0.63–2.61). No increase in incidence was observed from 2000–2006. MRSA was isolated in 1 menstrual and 3 non-menstrual cases (7% of TSS cases); 1 isolate was USA400. The superantigen gene tst-1 was identified in 20 (80%) of isolates and was more common in menstrual compared to non-menstrual isolates (89% vs. 50%, p = 0.07). Superantigen genes sea, seb and sec were found more frequently among non-menstrual compared to menstrual isolates [100% vs 25% (p = 0.4), 60% vs 0% (p < 0.01), and 25% vs 13% (p = 0.5), respectively].

Discussion: TSS incidence remained stable across our surveillance period of 2000–2006 and compared to past population-based estimates in the 1980s. MRSA accounted for a small percentage of TSS cases. tst-1 continues to be the superantigen associated with the majority of menstrual cases. The CDC case definition identifies the most severe cases and has been consistently used but likely results in a substantial underestimation of the total TSS disease burden.

Introduction

A syndrome of fever, myalgia, sore throat, edema, scarlatiniform rash, and desquamation associated with Staphylococcus aureus (SA) infection was first described in 1927, and in 1978 Todd et al. coined the term staphylococcal toxic shock syndrome (TSS) [1–2]. By 1980, young menstruating women using high absorbency tampons were identified as a high risk group, with cases also observed in men and non-menstruating women [3–4]. As the pathogenesis was better understood, it became clear that SA toxins called superantigens in conjunction with host susceptibility from the absence of anti-superantigen antibodies were risk factors for the development of TSS [5–6].

The estimated incidence of TSS in 1980 among young menstruating women was 13.7 per 100,000 persons [7]. Following multiple public health interventions including removal of highly absorbent tampons and messages regarding proper use of tampons, the number of cases declined sharply. By 1986 the rates of menstrual and non-menstrual TSS cases were 1 and 0.3 per 100,000, respectively [8–9]. In 1986, the overall case fatality rate
Described in USA400 [22]. USA400 have been described to carry disease burden of TSS. Surveillance Period 2000–2003

Methods

Many strains of SA are known to carry genes for superantigens including toxic shock syndrome toxin-1 (tst-1), the causative superantigen in most TSS cases [12–14]. Prevalent strains of SA are in constant flux. Over the past 15 years, community-associated methicillin-resistant SA (CAMRSA) strains, most notably USA300 and USA400, have emerged as predominant causes of skin and soft tissue infections in many geographic regions of the United States [15–16]. Skin and soft tissue infections are a common primary site of non-menstrual TSS [10,17]. Historically, children and adolescents had the highest prevalence of CAMRSA colonization and the highest incidence of CAMRSA infection, although more recently CAMRSA has been increasing in other age and risk groups such as hospitalized patients [18–20]. This is relevant because children have lower frequencies of protective anti-superantigen antibodies and are at greater risk to TSS if exposed to superantigen-producing SA strains [21]. The repertoire of superantigen genes produced by CAMRSA strains that are known to cause TSS is limited. The superantigen genes for staphylococcal enterotoxins A (sea), B (seb) or C (sec) have been described in USA400 [22]. seb has been associated with non-menstrual TSS cases [12,23–25]. However, neither USA300 nor USA400 have been described to carry tst-1 [13,25–26].

The current passive surveillance system for TSS is limited given the complexity of the clinical diagnosis and lack of a single diagnostic test. It is unclear whether the continually evolving epidemiology of circulating SA strains is leading to a change in the incidence of TSS cases. A report of a rapid increase in the number of SA isolates from patients with TSS submitted for superantigen testing during 2000–2003 to a Minneapolis-St. Paul metropolitan area reference laboratory suggested that rates of disease may be on the rise [27]. Given the possibility of an increase in the incidence of TSS, particularly among young persons in association with changes in SA epidemiology, we began active, population-based surveillance to identify the current incidence of TSS in the Minneapolis-St. Paul metropolitan area.

Surveillance Period 2000–2003

ICD-9 codes were used to identify potential cases of TSS. A list of all inpatient hospitalizations discharged between January 1, 2000 and December 31, 2003 that received at least one of the study codes was requested from all 24 hospitals in the MSP metropolitan area. All hospitals provided a list. Every hospitalization that received the specific ICD-9 code for TSS (040.92 or 040.89) was reviewed (Table 1). For hospitalizations that received at least one of the other ICD-9 codes (038.11, 038.19, 030.9, 785.50, 785.59 or 785.52), that were non-specific for TSS, a 20% random sample from within each hospital was reviewed. The medical records of all selected hospitalizations were reviewed for the Centers for Disease Control and Prevention (CDC) TSS case definition criteria (Table 2) [28] and other pertinent epidemiologic and clinical information. From 2000–2003 potential cases were also sought from Minnesota death certificates receiving the ICD-10 code for toxic shock syndrome (A48.3) and from cases reported to the Minnesota Unexplained Critical Illness and Death of Possible Infectious Etiology project (UNEX) [29]. Methods for surveillance from 2000–2003 were previously published [30].

Five experienced record abstractors received initial and ongoing training in data abstraction using a Minnesota Department of Health (MDH)-developed eight-page TSS case report form. TSS cases were classified as menstrual if (i) the onset of symptoms was during documented dates of menstruation or (ii), in the absence of documented dates of menstruation, a woman was between the ages of 15 and 54 years and a vaginal culture was positive for SA. All other TSS cases were classified as non-menstrual.

Surveillance Period 2004–2006

Based on preliminary analysis of 2000–2003, the TSS-specific code identified cases with higher sensitivity and specificity compared to other codes and therefore only the TSS-specific code was used for surveillance period of 2004–2006 [30]. A list of all inpatient hospitalizations discharged between January 1, 2004 and December 31, 2006 that received the TSS-specific code was requested from all 24 hospitals in the MSP metropolitan area; all hospitals complied. All hospitalizations were reviewed using the same methodology as used during the surveillance period 2000–2003.

Population Denominator Calculations

Population estimates were taken from the 2000 US Census and the inter-Census estimate for 2005. Assuming a linear rate of

Table 1. ICD-9 Study Codes Utilized for TSS Case Ascertainment.

| ICD-9 Code   | Associated Diagnosis                  |
|--------------|--------------------------------------|
| Specific toxic shock syndrome code |                                      |
| 040.89 or 040.82* | Toxic shock syndrome                |
| Non-specific toxic shock syndrome codes |                                    |
| 038.11 | Staphylococcus aureus septicemia       |
| 038.19† | Other staphylococcal septicemia      |
| 038.9 | Unspecified septicemia               |
| 785.50 | Shock without mention of trauma      |
| 785.59 or 785.52* | Sepsis                           |

*The ICD-9 code number assigned to “toxic shock syndrome” changed from 040.89 to 040.82 on October 1, 2002, and the code number assigned to “sepsis” changed from 785.59 to 785.52 on October 1, 2003. While the numeric codes changed, their associated diagnoses remained unchanged and are considered mutually exclusive.

†Code eliminated after interim analysis.
Table 2. Surveillance Case Definition of TSS [28].

| Clinical Criteria |
|-------------------|
| 1. Fever: temperature ≥ 38.9°C (102.0°F). |
| 2. Rash: diffuse macular erythoderma. |
| 3. Desquamation: 1–2 weeks after onset of illness, particularly on the palms and soles. |
| 4. Hypotension: systolic blood pressure (BP) ≤ 90 mmHg for adults or less than fifth percentile by age for children aged <16 years; orthostatic drop in diastolic blood pressure ≥ 15 mmHg from lying to sitting, orthostatic syncope, or orthostatic dizziness. |
| 5. Multisystem involvement (three or more of the following): |
| • Gastrointestinal: vomiting or diarrhea at onset of illness. |
| • Muscular: severe myalgia or creatine phosphokinase (CPK) level at least twice the upper limit of normal (ULN). |
| • Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia. |
| • Renal: blood urea nitrogen (BUN) or creatinine (Cr) at least twice ULN for laboratory or urinary sediment with pyuria (≥ 5 white blood cells [WBC] per high-power field) in the absence of urinary tract infection. |
| • Hepatic: total bilirubin (T.Bili), alanine aminotransferase enzyme (ALT), or asparate aminotransferase enzyme (AST) levels at least twice ULN for laboratory. |
| • Hematologic: platelets ≤ 100 x 109/L. |
| • Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent. |

Laboratory criteria

6. Negative results on the following tests, if obtained:

• Blood, throat, or cerebrospinal fluid cultures (blood culture may be positive for Staphylococcus aureus).

Rise in titer to Rocky Mountain spotted fever, leptospirosis, or measles.

Case classification

Probable case: meets the laboratory criteria and in which four of the five clinical findings described above are present.

Confirmed case: meets the laboratory criteria and in which all five of the clinical findings described above are present, including desquamation, unless the patient dies before desquamation occurs.

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Statistical Analysis

Cases of TSS with a home zip code outside the MSP area were included in the descriptive analysis of cases but were excluded from incidence estimations, as referral patterns strongly favor cases with home zip codes in the MSP area to be hospitalized in the MSP area [22/23, (96%) compared to menstrual cases [22/23, (96%) compared to menstrual cases]. For menstrual cases, the denominator was females aged 13–55 years, as this was the approximate age distribution among menstrual cases.

Frequentist Poisson regressions were performed using SAS 9.2 to corroborate Bayesian analysis and to calculate P-values for test of trend.

To assess a change in incidence over the years 2000–2006 only those cases identified using the TSS specific code were used. Frequentist Poisson regression was used to calculate P-values for test of trend across time.

Characterization of isolates

All available SA isolates from confirmed or probable cases were collected. Isolates were tested by PCR for presence of superantigen genes tst-1, sea, seb, and sei [32]. Molecular typing of a limited number of isolates was performed by pulsed field gel electrophoresis (PFGE) of genomic DNA after restriction endonuclease digestion with Sma1. PFGE patterns were compared using Bionumerics Software34 and the Dice coefficient. USA clonal groups were determined by PFGE per SA PFGE genotype nomenclature [33]. Antimicrobial susceptibility testing was performed by clinical laboratories.

Results

Case Identification

From January 1, 2000 to December 31, 2003, we identified 7,414 hospitalizations with at least one study code and 43 probable or confirmed TSS cases, all from ICD-9 code surveillance (Figure 1). Cases were identified at 14 of the 24 hospitals, with 89% of cases at five hospitals. From 2000–2003, no additional cases were identified from 9 deaths coded with the ICD-10 code for TSS and from the 153 reported UNEX cases. Among the 43 cases from 2000–2003, the TSS-specific code was more likely to be used on menstrual cases [22/23, (96%)] compared to between age groups and across time.
non-menstrual cases [16/20, (80%), p = 0.17]. From January 1, 2004 to December 31, 2006, an additional 77 hospitalizations receiving the TSS-specific code were identified (Figure 1) of which 18 were probable or confirmed TSS cases. The total number of TSS cases identified over years 2000–2006 was 61.

Clinical Characteristics
Among the 61 TSS cases, the median age was 21.4 years (range, 1.4–81.0). The median age was 34.8 years (range, 4.5–81) for the 13 males and 18.5 years (range, 1.4–76.5) for the 48 females (male vs. female cases, p = 0.05). There were 33 menstrual and 28 non-menstrual TSS cases, with menstrual cases trending toward younger age and fewer preexisting conditions (Table 3). There were minimal differences in clinical presentation between menstrual and non-menstrual cases.

Of the 28 non-menstrual cases, 13 (46%) had a skin or soft tissue infection, of which 4 (31%) were post-surgical. Additionally, 10 (36%) had no primary source identified after a median of 4 (range 1, 6) sites cultured, 1 had multiple positive culture sites, 3 had primary bacteremia, 1 had a pulmonary primary site, and 1 a urinary tract site.

All cases were treated with antimicrobial agents, with 58 (95%) receiving a beta-lactam, 41 (67%) clindamycin, and 30 (49%) vancomycin. There was no significant difference in the use of beta-lactams, clindamycin, or vancomycin between menstrual and non-menstrual cases. Nine percent of cases were treated with activated protein C (APC), and 19% were treated with intravenous immunoglobulin (IVIG). Length of hospitalization was shorter in menstrual cases compared to non-menstrual cases (median, 5 vs. 11 days, p<0.001). Cases treated with clindamycin were younger versus those not treated with clindamycin (median 18 vs. 40 years p = 0.02) but there was no difference in the length of hospitalization (6.5 vs. 6.0 days p = 0.67). There were no significant differences in age, sex, number with multiple organ system involvement, or length of hospitalization between TSS cases treated with IVIG versus no IVIG, APC versus no APC, a beta-lactam versus a different antimicrobial agent, and vancomycin versus a different antimicrobial agent. One death (2%) occurred in an 80-year old male.

Menstrual cases from January 1, 2000 to June 30, 2003 (n = 19) were compared to July 1, 2003 to December 31, 2006 (n = 14). There was no significant difference in the frequency of underlying health conditions, age, length of hospitalization, number of positive cultures for SA or MRSA, or treatment with IVIG, APC, beta-lactam antimicrobials, or clindamycin between these two time periods. Vancomycin was prescribed more frequently in July 1, 2003 to December 31, 2006 compared to January 1, 2000 to June 30, 2003 (64% vs. 21% p = 0.03).
Table 3. Description of Toxic Shock Syndrome Cases.

| Characteristics                                | All Cases | Menstrual | Non-menstrual | p value* |
|------------------------------------------------|-----------|-----------|---------------|----------|
| Median age (yr)                                | 21.4 (1.4–81.0) | 17.9 (12.4–52.6) | 26.3 (1.4–81.0) | 0.12     |
| Female sex                                     | 48 (79%)  | 33 (100%) | 15 (54%)      | <0.001   |
| MSP area home zip code                         | 50 (82%)  | 28 (85%)  | 22 (79%)      | 0.74     |
| Median days from first symptom to hospitalization | 2 (0–7)    | 2 (0–7)   | 2 (0–7)       | 0.65     |
| One or more co-morbidities†                    | 19 (31%)  | 7 (21%)   | 12 (43%)      | 0.10     |
| All six criteria                               | 12 (20%)  | 9 (27%)   | 3 (11%)       | 0.12     |
| Temperature ≥38.9°C (102.0°F)                  | 59 (97%)  | 32 (97%)  | 27 (96%)      | 1.00     |
| Hypotension‡                                   | 57 (93%)  | 32 (97%)  | 25 (89%)      | 0.33     |
| Rash consistent with erythroderma              | 60 (98%)  | 32 (97%)  | 28 (100%)     | 1.00     |
| Desquamation                                   | 20 (33%)  | 12 (36%)  | 8 (29%)       | 0.59     |
| Multisystem involvement‡                       | 60 (98%)  | 32 (97%)  | 27 (96%)      | 0.46     |
| Any culture positive for SA                    | 44 (72%)  | 28 (85%)  | 16 (57%)      | 0.02     |
| Median days of hospitalization                 | 6 (2–50)  | 5 (2–25)  | 11 (2–50)     | <0.001   |
| Deaths                                         | 1 (2%)    | 0 (0%)    | 1 (4%)        | 0.46     |

Abbreviations: yr, years; MSP, seven-county Minneapolis-St. Paul metropolitan area; SA, Staphylococcus aureus; MRSA, Methicillin-Resistant SA; MDH, Minnesota Department of Health.

The incidence of TSS in Minnesota has declined substantially since the first population based estimates in 1980. The greatest average annual incidence was estimated based on 2000–2003 surveillance. Seven TSS cases from 2000–2003 (all with the specific TSS code) were excluded because they had home zip codes outside of the study area, leaving 31 cases with the TSS-specific ICD-9 code. Five cases were identified using the non-specific TSS codes obtained from the 20% sample of hospitalizations adding 23 additional cases for a total of 56 estimated cases from 2000 through 2003. Average annual incidence per 100,000 persons of all TSS cases was 0.52 cases (95% CI, 0.32–0.77), of menstrual cases was 0.69 (95% CI, 0.59–1.16), and of non-menstrual cases was 0.32 (95% CI, 0.12–0.67) (Table 5). Women aged 13–24 years had the highest incidence with an annual rate of menstrual TSS of 1.41 cases per 100,000 (95% CI, 0.63–2.61).

For purposes of determining if a change in annual incidence was occurring over the years 2000–2006, the annual incidence was estimated from cases that were coded with the TSS-specific code as this was conducted consistently over this time frame. Over the years 2000–2006, the annual incidence rate of all TSS, menstrual TSS, and non-menstrual TSS did not change significantly (test of trend p = 0.63, p = 0.71, and p = 0.77 respectively). When stratifying menstrual and non-menstrual TSS by dichotomous age groups of less than or equal to 24 years and greater than 24 years, there was no significant change in the incidence among the younger menstrual TSS group (test of trend p = 0.22) and younger non-menstrual TSS group (test of trend p = 0.69) over the years 2000–2006 (Figure 2). Similarly the older non-menstrual group did not have a significant change in the annual incidence (test of trend p = 0.40), but older menstrual TSS group had a significant decrease in the annual incidence (test of trend p = 0.02).

Discussion

The incidence of TSS in Minnesota has declined substantially since the first population based estimates in 1980. The greatest...
Table 4. Comparison of Susceptibility Patterns and Superantigens among Isolates Associated with Menstrual and Non-menstrual Toxic Shock Syndrome Cases.

| Antimicrobial (n = 44) | All Cases | Menstrual | Non-menstrual | p value* |
|-----------------------|-----------|-----------|---------------|----------|
| penicillin (n = 35)   | 39/44 (88%) | 25/28 (89%) | 14/16 (88%)  | 1.00     |
| erythromycin (n = 35) | 0/35 (0%) | 0/24 (0%) | 0/11 (0%) | 1.00     |
| clindamycin (n = 36) | 23/35 (66%) | 16/24 (67%) | 7/11 (64%) | 1.00     |
| oxacillin (n = 38)    | 31/36 (83%) | 21/24 (88%) | 10/12 (83%) | 1.00     |
| vancomycin (n = 34)   | 34/34 (100%) | 24/24 (100%) | 10/10 (100%) | 1.00     |
| quinolones (n = 34)   | 32/34 (94%) | 22/23 (96%) | 10/11 (91%) | 1.00     |
| gentamicin (n = 19)   | 19/19 (100%) | 16/16 (100%) | 3/3 (100%) | 1.00     |
| TMP/SMX (n = 33)      | 32/33 (97%) | 22/23 (96%) | 10/10 (100%) | 1.00     |

Abbreviations: TMP/SMX, trimethoprim-sulfamethoxazole; tst-1, toxic shock syndrome toxin 1; sea, staphylococcal enterotoxin; seb, staphylococcal enterotoxin B; sec, staphylococcal enterotoxin C.

*Comparison of menstrual and non-menstrual TSS cases. Fisher’s Exact Chi-Square test comparing menstrual and non-menstrual isolates.
†Includes inducible clindamycin resistance as evidenced by D-test.
*Testing was performed on gatifloxacin, ciprofloxacin, or levofloxacin based on clinical laboratory. If more than one quinolone was tested, isolate was classified as susceptible if the all quinolones tested were susceptible.
†Both cases that where sea positive were also tst-1 positive.

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Table 5. Average Annual Toxic Shock Syndrome Incidence by Age and Gender Groups During the Period of Most Complete Case Ascertainment, 2000–2003.

| Risk Group | Annual Incidence* |
|------------|-------------------|
|            | per 100,000 Persons at Risk (95% CI) |
| All TSS    | 0.52 (0.32–0.77)  |
| All Males  | 0.23 (0.10–0.44)  |
| All Females| 0.79 (0.48–1.22)  |
| All Menstrual TSS (age 13–54 yr) | 0.69 (0.39–1.16) |
| Menstrual age 13–24 yr | 1.41 (0.63–2.61) |
| Menstrual age 25–54 yr | 0.43 (0.19–0.82) |
| All Non-menstrual TSS | 0.32 (0.12–0.67) |
| Non-menstrual females ≤24 yr | 0.36 (0.12–0.87) |
| Non-menstrual females >24 yr | 0.36 (0.14–0.82) |

Abbreviations: CI, Bayesian confidence interval; TSS, toxic shock syndrome; yr, year.
*Annual incidence averaged over all study years, 2000–2003 and estimated by Bayesian statistical methods and Poisson regression.

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Figure 2. Annual incidence of menstrual and non-menstrual TSS across years 2000–2006. Annual incidence of TSS across years 2000–2006 of menstrual (A) and non-menstrual (B) TSS stratified by age ≤24 and >24 years using only cases receiving the TSS specific ICD-9 code. Error bars represent 95% confidence limits. Frequentist Poisson regressions were used to calculate P-values for test of trend. Over years 2000–2006 among menstrual TSS aged ≤24 years test of trend was not significant (p = 0.22) as was non-menstrual age ≤24 years (p = 0.69) and >24 years (p = 0.40). There was a significant decreasing annual incidence over 2000–2006 in menstrual TSS aged >24 years (test of trend p = 0.02).

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surveillance period, the median age for all cases was 21 years, and for menstrual cases was 18 years. Cases stayed a median of 6 hospital days including intensive care unit time. While most recover, we identified one death due to TSS. Despite public health efforts, such as removal of high-absorbency tampon products and public safety announcements, menstrual TSS continues to occur at rates similar to other infections of public health importance such as *N. meningitidis* (annual incidence 0.28/100,000) [30] and invasive group A *Streptococcus* (annual incidence 3.6/100,000) [39].

Unfortunately, no single diagnostic test is available to clearly identify persons with TSS. Using the CDC case definition we identified one death due to TSS. Despite public health efforts, such as removal of high-absorbency tampon products and public safety announcements, menstrual TSS continues to occur at rates similar to other infections of public health importance such as *N. meningitidis* (annual incidence 0.28/100,000) [30] and invasive group A *Streptococcus* (annual incidence 3.6/100,000) [39].

Interestingly, there was a decrease in the rates of menstrual TSS among women older than 24 years when comparing rates of disease over the years 2000–2006. Possible factors leading to a decreasing incidence include decreasing tampon use, increasing levels of protective antibody in this population, or decreasing use of intravaginal contraceptive devices. An additional protective factor may be the increasing frequency of menstrual suppression techniques within this group, as the safety and acceptability of this practice among patients and practitioners has increased in the last decade [41–42]. The prevalence of menstrual suppression among women of any age group is unknown.

We conducted this study within a single geographic area. While there is racial and ethnic diversity in the MSP area, it may not be representative of the racial and ethnic makeup of other geographic areas and there may be unknown factors unique to this region. Additionally, a select group of ICD-9 codes were used to capture cases. If additional, lower yield codes had been included, we may have identified additional TSS cases. Therefore, our calculated incidence likely represents a low estimate of the actual incidence.

In conclusion, we observed a stable incidence of both menstrual and non-menstrual TSS in the years 2000–2003 compared to the late 1980s, with the highest incidence among women aged 13–24 years. There was also no significant increase in annual TSS incidence over the years 2000–2006. While one TSS case due to CAMRSA (USA400) was identified, the increased prevalence of CAMRSA in Minnesota did not appear to affect the incidence of menstrual or non-menstrual TSS. It would be useful to conduct surveillance for TSS cases in other populations and geographic areas that may have different prevalent staphylococcal strains and host susceptibilities to TSS, as well as assess the toxins produced by implicated strains in order to monitor changes in the epidemiology of TSS.

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Author Contributions

Conceived and designed the experiments: AD LL PS TR RD RL. Performed the experiments: AD LL TR LV PS. Analyzed the data: AD LL TR LV RD RL. Contributed reagents/materials/analysis tools: AD LL PS TR. Wrote the paper: AD.

incidence over 2000–2006 in menstrual TSS aged
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