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Research Article

Cases of Menstrual Toxic Shock Syndrome in the Czech Republic in 1997–2022

Petr Petráš*, Michaela Šimková, Jana Kekláková, Radka Hutníková, and Jan Bílý

[1]*National Reference Laboratory for Staphylococci, National Institute of Public Health, Prague, Czech Republic*

Abstract

Staphylococcal toxic shock syndrome (TSS) is a serious condition that can be life threatening. There are two forms of this disease: menstrual and non-menstrual. In the 25 years from 1997 to 2022, 105 cases of TSS related to menstruation were registered at the National Reference Laboratory for Staphylococci of the National Institute of Public Health (NIPH) in Prague. All the patients recovered, but one third of the them had a severe course of the illness including intensive care unit admission reported in their discharge summaries. All the patients except for one had a history of vaginal tampon use, in the remaining one it was a menstrual cup.

The article characterises toxigenic *S. aureus* strains that were confirmed as the causative agents of these diseases. The most common were TSST-1 producers in combination with enterotoxin – usually type A (65 strains, 61.9%). The TSST-1 toxin exclusively was produced by 33 strains, seven strains (6.6%) were confirmed positive for only one type of enterotoxin. In one case in 2011, *S. aureus* positive for enterotoxin H was isolated as the causative agent. Except for one case, these always were MSSA strains.

Due to the large spectrum of possible symptoms of the TSS disease, establishing a clinical diagnosis can be difficult. This may be facilitated by confirmation of staphylococcal toxin aetiology.

***Corresponding author**

Petr Petráš, National Reference Laboratory for Staphylococci, National Institute of Public Health, Šrobárova 48, 100 42 Prague, Czech Republic; Tel: 420 267 082 264

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Keywords

- Staphylococcal toxic shock syndrome (TSS)
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- *Staphylococcus aureus* toxins
- TSST-1
- Staphylococcal enterotoxin

ABBREVIATIONS

TSS: Staphylococcal Toxic Shock Syndrome; NRL/St: National Reference Laboratory for Staphylococci; NIPH: National Institute of Public Health; TSST-1: Toxic shock syndrome toxin-1; SE: Staphylococcal Enterotoxin; MSSA: Methicillin sensitive *Staphylococcus aureus*

INTRODUCTION

Toxic Shock Syndrome (TSS) is a multisystem disease, in severe cases even life-threatening. The aetiological agents are strains of *Staphylococcus aureus* that produce the toxic shock syndrome toxin TSST-1 and/or staphylococcal enterotoxin. These toxins belong to the group of bacterial superantigens. These are antigens that do not require processing by antigen presenting cells for their interaction with the immune system, but bind directly to T cell (lymphocyte) receptors and activate the immune system by an uncontrolled response [1].

Another cause of toxic shock syndrome may be toxinogenic strains of *Streptococcus pyogenes*, with production of pyrogenic toxins, which are also classified as superantigens.

TSS is characterized by:

- high temperature (≥ 38.9 °C);
- some form of skin rash (from petechiae to scarlatiniform rash);
- rapid decrease in blood pressure (≤ 90 mm systolic);
- peeling of the upper layers of the epidermis, which appears about 2 weeks after the first symptoms.

In addition to these, other complications, such as disorders of gastrointestinal and central nervous systems and muscular, mucosal, renal, hepatic and circulatory disorders, are usually present (Case definition - CDC 2011 [2], update 2022 [3]).

TSS has two forms: the first one is associated with menstruation. Risk factors are vaginal carriage of toxigenic strains, some form of immune deficiency, and use of vaginal tampons. The second, non-menstrual form, can be a complication of any staphylococcal disease where the *S. aureus* strain has the opportunity to multiply and produce sufficient amount of toxin.

This infection then has the same symptoms as menstrual TSS. According to the records of our laboratory, the most frequent cases are pyoderma, early post-traumatic infections, post-operative infections and burns [4].

TSS was first described in 1978 by paediatrician Todd [5], in 7 children. Subsequently, it proved to be an infection primarily associated with menstruation and the use of vaginal tampons, especially the types with high absorption capacity [6]. The incidence is low, usually reported as 0.5 cases/100,000 persons per year or 6/100,000 menstruating women per year [7]. However, it is a very serious disease where the staphylococcal aetiology must be recognized quickly and appropriate treatment selected. Due to the diverse spectrum of symptoms, clinical diagnosis can sometimes be difficult.

In this paper, we present a review of 105 cases of menstrual form of TSS that we registered at the National Reference Laboratory for Staphylococci of the NIPH Prague (NRL/St) between December 1997 and December 2022, and by establishing the toxigenicity of the submitted *S. aureus* strain, we were able to contribute to the confirmation of the A48.3 clinical diagnosis, according to the International Classification of Diseases.

MATERIALS AND METHODS

Strains

A total of 105 *S. aureus* strains isolated in association with menstrual TSS were sent to the NRL/St to examine TSST-1 and enterotoxin production from all 14 regions of the Czech Republic, including the Prague region, in the period 1997–2022. The majority of the isolates were isolates from vaginal swabs, in some cases the strain was isolated from a vaginal tampon and in one case from a menstrual cup.

Identification of *S. aureus* strains

It is performed by means of a screening test for the clumping factor (Pastorex Staph Plus, BioRad) and detection of hyaluronidase [8]. We genetically confirm *S. aureus* subsp. *aureus* by detecting the presence of the *nuc* gene encoding thermostable nuclease production by PCR [9]. Since 2011, we also identify staphylococcal strains by MALDI-TOF mass spectrometry, which can reliably confirm *S. aureus* strains.

Detection of staphylococcal toxins

In 1997–2016, we demonstrated the toxigenicity of TSST-1 and enterotoxins (SE) A–D by reverse passive latex agglutination using commercial TST-RPLA and SET-RPLA kits by Denka Seiken. The sensitivity of these tests is 1 ng toxin/ml.

Since 2017, we have been screening for the presence of genes encoding the respective toxins by PCR [10,11]. Currently, these are genes for TSST-1 and the main enterotoxins A - D. In case of a negative result for these virulence factors, we detect the presence of genes for even more enterotoxins: SEE, SEG, SEH, SEI, SEK, SEL, SEM, SEP and the "like-enterotoxin" SElJ.

Sensitivity *S. aureus* strains to oxacilin

The PCR method was used to monitor the presence of the *mecA* gene, which encodes the production of the alternative penicillin-binding protein PBP 2a [12] responsible for resistance to oxacillin and other beta-lactam antibiotics.

RESULTS

Between 1997 and 2022, we confirmed the ability to produce TSST-1 or enterotoxin in 105 *S. aureus* strains isolated in association with menstrual TSS. Figure 1 presents the distribution of these aetiological agents according to the positivity of each toxin. The most common were TSST-1 producers in combination with enterotoxin – usually type A (65 strains, 61.9%). 33 strains (31.4%) were positive exclusively for TSST-1 toxin. Seven strains were individually confirmed positive only for enterotoxin: two for SEB, two for SEC, one strain each for SEA, SEH, and once for the combination SEA+SEB (Table 1).

Figure 2 shows the patient age distribution. The youngest was a 12-year-old girl, the oldest a 37-year-old woman. The mean age of the patients was 20 years, the median was 18 years.

S. aureus strains were most frequently isolated from vaginal swabs: 74 strains (70.4%), 24 isolates (22.8%) were from vaginal tampons. The "other" set included isolates from haemoculture, faeces, nasal swabs and one strain recovered from a menstrual cup (Figure 3).

Figure 4 shows the distribution of hospital locations from the Clinical Microbiology Departments of which strains *S. aureus* were sent as agents of the menstrual form of TSS. A total of 105 strains were sent from 14 regions of the Czech Republic, with the largest number of strains coming from the South Bohemia region (28 strains), the Pilsen region (18 strains), and the Capital City of Prague (15 strains).

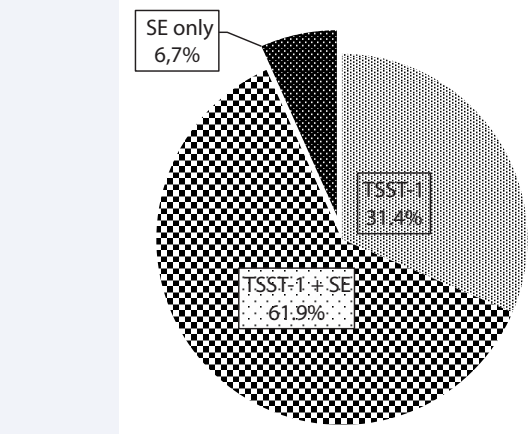

Figure 1 Toxigenicity of *S.aureus* strains from the 105 cases of menstrual TSS in the Czech Republic since 1997 to the end of 2022 (TSST-1= Toxic Shock Syndrome Toxin-1; SE = staphylococcal enterotoxin).

Table 1: Toxin production in the 105 strains of *S. aureus* that caused menstrual TSS in the Czech Republic in 1997–2022

Toxin production	TSST-1 only	TSST-1 + enterotoxin (SE)			enterotoxin (SE) only				
	TSST-1	TSST-1 + SEA	TSST-1 + SEC	TSST-1 + SEB + SEC	SEA	SEB	SEC	SEH	SEA + SEB
number of strains	33	56	6	3	1	2	2	1	1
%	31.4%	61.9%			6.7%				

TSST-1: Toxic shock syndrome toxin-1; **SE**: Staphylococcal enterotoxin (type A, B. C, H)

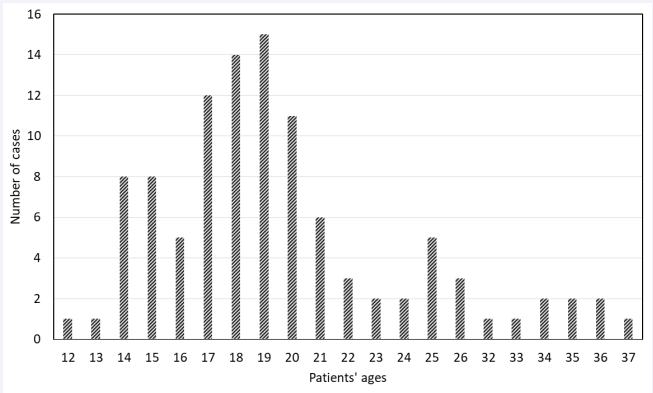

Figure 2 Numbers of menstrual TSS cases by age of patients in the Czech Republic 1997–2022 (n = 105).

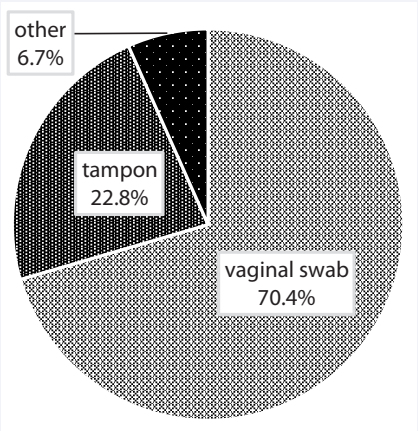

Figure 3 Isolation of aetiological agents of menstrual TSS, toxinogenic strains of *S. aureus* (n = 105) in the Czech Republic 1997–2022.

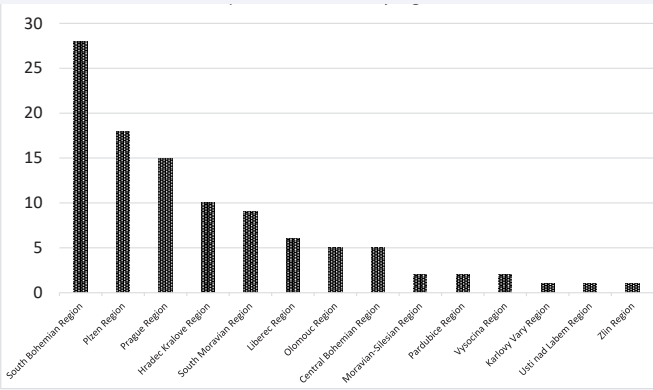

Figure 4 Distribution of the 105 cases of menstrual TSS in the Czech Republic 1997–2022 by region.

In relation to menstrual TSS, we received an average of 4 strains per year for the entire 25 years. Years 2010 and 2018 were exceptional in this respect as we received 12 and 10 strains.

With one exception, all the *S. aureus* strains were sensitive to oxacillin. Resistance was detected in only one strain from 2010, which caused severe TSS in a 14-year-old girl, including a one-week stay in intensive care.

DISCUSSION

For the 105 cases of menstrual TSS registered over the entire period (1997–2022), we used a simple form to obtain information from which we could verify that the diagnosis really was A48.3 [3]. In about 2/3 of the cases we also obtained more detailed information about the course of the disease. It showed that in 38% of the patients a severe course was described, and 30% of the patients were admitted to intensive care. All these cases ended in recovery, but lethal ends of menstrual TSS have been reported in literature [13].

S. aureus strains positive for TSST-1 were mostly confirmed as the aetiological agents, either alone or in combination with some type of enterotoxin (total of 98 cases, 93.3%). In 7 cases (6.6%) the causative strain was *S. aureus* with enterotoxin production only. This is in accordance with literature, where it is reported that in the menstrual form of TSS, 90% of the aetiological agents are TSST-1-producing strains, whereas in the non-menstrual form, a higher percentage of strains toxigenic only to some type of enterotoxin are reported [14] (Figure 1,Table 1).

The distribution of menstrual TSS cases according to the location of the hospitals from which we obtained the strains and clinical information is very uneven. From 3 regions, there were only two cases each, and only one case was registered in the other three regions in the entire 25 years (Figure 4). It is obvious that this serious disease is not paid adequate attention.

From the microbiological point of view, an interesting case was the illness of a 36-year-old female patient who was admitted to the ICU of the Hradec Kralove hospital in 2011. It was a classic course of menstrual TSS, including febrile, maculopapular exanthema, hypotension and other symptoms (diarrhoea, vomiting, abdominal pain, leukopenia, thrombocytopenia). In the aetiological agent, a strain of *S. aureus* isolated from the vaginal swab and vaginal tampon, the NRL/St detected the presence of the *seh* gene, encoding the production of enterotoxin H. After complex treatment, including antibiotics clindamycin and gentamicin, the patient recovered after 10 days and was discharged to home care. During subsequent outpatient follow-up, epidermal peeling of the palms was noted.

Finally, we present a short case report of menstrual TSS from South Bohemia from 2003, when acute abdomen was initially suspected and appendectomy was performed.

The patient, a 14-year-old girl, was brought to the surgical ward for right lower abdominal pain. She was afebrile at the time, with no inflammatory parameters. Applying ice and a follow-up appointment the next day was recommended. Due to increasing abdominal pain, she was brought back to hospital in the evening and admitted for observation in the paediatric ward. The following day, the pain persisted, temperature rose and inflammatory parameters increased. Laparoscopic revision of the small pelvis was indicated by the surgeon and performed the same day. An appendectomy was performed, but the appendix was macroscopically free of signs of inflammation. During preoperative preparation in the paediatric ward, the nurse detected in the girl and removed a vaginal tampon (day 5 of menses). The following day, the patient's condition worsened, including an increase in temperature to 39°C and a further increase in inflammatory parameters. A macular pruritic exanthem appeared on the abdomen and later on the extremities, which was at first considered allergic given the anamnestic data. After the general evaluation, staphylococcal toxin aetiology was suspected, a vaginal swab was taken for culture and parenteral clindamycin and gentamicin were administered. The next day, a massive finding of *S. aureus* in the vagina was confirmed and the strain was sent to the NRL/St. The following day, the strain was reported positive for TSST-1 and enterotoxin A production by our laboratory. The treatment worked, the patient's condition began to improve rapidly, and she was discharged home in good condition after 9 days of hospitalization. 14 days after the onset of the illness, the girl developed significant skin peeling on her hands and feet, which was the last clinical marker confirming the A48.3 diagnosis.

All patients but one had a history of vaginal tampon use. This is a clearly identified risk factor in the microbiological-epidemiological literature. The remaining patient used a menstrual cup, which has also been reported in the literature in association with menstrual TSS [15,16].

CONCLUSION

Toxic shock syndrome is a severe multi-organ staphylococcal disease. All the patients out of the 105 cases of menstrual TSS presented recovered, but sometimes the course was very severe, including a stay in the intensive care unit. Except for one, all the cases had a history of vaginal tampon use, which is clearly a risk factor. In the last case, a menstrual cup was used. In toxic shock syndrome it is very important to quickly establish the staphylococcal toxin aetiology so that adequate treatment can be used.

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