Menstrual toxic shock syndrome: case report and systematic review of the literature

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Menstrual toxic shock syndrome (mTSS) is a life-threatening disease caused by superantigen-producing *Staphylococcus aureus*. Incidence ranges from 0·03 to 0·50 cases per 100 000 people, with overall mortality around 8%. In this Grand Round, we present the case of a previously healthy 23-year-old menstruating woman who was diagnosed with mTSS after she presented at our hospital with a septic condition for the second time. The diagnosis was confirmed by fulfilment of the clinical criteria outlined by the US Centers for Disease Control and Prevention (CDC; fever, rash, desquamation, hypotension, and multi-system involvement) as well as a nasal swab positive for the *S aureus* strain and presence of the gene encoding for toxic shock syndrome toxin 1 (TSST-1). In the early 1980s, when mTSS was first described, use of tampons was considered the main risk factor. Today, the complex interplay between pathogenic factors of *S aureus*, immunological mechanisms of the host, and changes in the vaginal ecosystem during menstruation has broadened current understanding of the disease, and the CDC criteria have appreciable limitations in everyday clinical practice.

Lancet Infect Dis 2019; 19: e313–21

Published Online May 28, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30041-6

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Introduction

Menstrual toxic shock syndrome (mTSS) is a rare but life-threatening disease with high morbidity and mortality, first described by Todd and Fishaut in 1978.[1] The clinical onset is characterised by fever, hypotension, and early multi-organ deterioration, as well as desquamation of the skin on average 8–12 days afterwards.[2]

Since the recognition of toxic shock syndrome (TSS) in the late 1970s, progress has been made in defining the disease. Superantigen-producing *Staphylococcus aureus* has been identified as causative bacterial agent. mTSS and non-menstrual-associated TSS (non-mTSS) have been recognised as two different entities with the same clinical picture. And the US Centers for Disease Control and Prevention (CDC) proposed diagnostic criteria, among other things, defining TSS as menstruation-associated when its onset is less than 4 days before the start of menses.[3] Revised diagnostic criteria were published by the CDC in 2011 (panel 1).[3]

Treatment of mTSS is often delayed due to misdiagnosis, highlighting the importance of awareness of the disease among health-care professionals. In this Grand Round we review the literature published between 1978 and 2018 and present the case of a 23-year-old menstruating woman who was diagnosed with mTSS after presenting at our hospital with a septic condition a second time.

Case description

A previously healthy 23-year-old menstruating woman was re-evaluated in our emergency department for a second episode of high fever, nausea, and malaise. She had been admitted 3 weeks earlier with a septic condition and suspected urogenital infection with concomitant nausea.

At the time of the first admission, laboratory findings included leucocytosis ($14·2\times10^9$ cells per L) with lymphopenia in the differential blood count, increased C–reactive protein (132 mg/L, normal <5 mg/L), normal blood urea (4·1 mmol/L, normal 2·5–6·4 mmol/L), and slightly elevated creatinine (95 µmol/L, normal 49–90 µmol/L). During her hospital stay of 5 days, the patient had persistent hypotension requiring massive amounts of intravenous fluids (13 L Ringer's lactate) for haemodynamic stabilisation. The patient was given empirical therapy with ceftriaxone and single-dose

***Panel 1*: Case definition according to the US Centers for Disease Control and Prevention[3]**

Clinical criteria

- Fever: temperature greater than or equal to 102·0°F (greater than or equal to 38·9°C)
- Rash: diffuse macular erythroderma
- Desquamation: 1–2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children younger than 16 years
- Multi-system involvement—ie, three or more of gastrointestinal (vomiting or diarrhoea at onset of illness), muscular (severe myalgia or creatine phosphokinase level at least twice the upper limit of normal), mucous membrane (vaginal, oropharyngeal, or conjunctival hyperaemia), renal (blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria [greater than or equal to five leucocytes per high-power field] in the absence of urinary tract infection), hepatic (total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory tests), haematological (platelets less than 100 000 per µL), or central nervous system (disorientation or altered consciousness without focal neurological signs in the absence of fever or hypotension)

Laboratory criteria

- Negative results of blood, throat, or cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*; negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles)

Case classification

- Probable: a case that meets the laboratory criteria and in which four of the five clinical criteria described above are present
- Confirmed: a case that meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

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tobramycin for suspected Gram-negative invasive infection. On day 3 of the first hospital admission, she developed a fine, transient rash on her cleavage and legs, an episode of diarrhoea that lasted 2 days, and diffuse epigastric pain as well as a white-coated tongue, all of which had been attributed to the current antibiotic treatment. Blood cultures obtained upon admission and a stool culture obtained on day 4 were negative for Gram-negative infection. Urine culture indicated a normal microbiome. A throat swab was negative for influenza and β-haemolytic streptococcus. Based on her improved condition, the patient was discharged and treated with oral ciprofloxacin for another 7 days. Her discharge diagnosis was sepsis with unknown focus, potentially a developing urinary tract infection with urosepsis.

On presenting for the second time in the emergency department the patient reported the same non-specific symptoms (including malaise, and myalgia and fever for 1 day) without a clear focus of infection. Her only regular medication was an estriadol-containing oral contraceptive producing a regular menstrual cycle for 28 days, with 5–6 days of bleeding. Her medical history revealed that the symptoms occurred on both occasions while she was menstruating: on day 5 in the first episode, and 2 days after menstruation in the second. The patient reported using OB procomfort tampons with normal absorbency, and changing every 3–4 h while awake, but less often at night and while sleeping. 2 days before admission she switched to sanitary napkins because of decreasing blood flow. The patient denied suffering any vaginal discomfort. She confirmed the onset of palmoplantar desquamation of her hands 10 days after the previous discharge from hospital.

On the second admission, the patient presented with fever (38·4°C) and was normotensive and tachycardic. No cardiac, pulmonary, or abdominal abnormalities were noted on physical examination and no rash was visible, other than fine desquamation of the proximal palmar fingers of both hands. The rest of the examination was otherwise unremarkable.

Laboratory studies showed a leucocyte count of $14 \cdot 2 \times 10^9$ cells per L with a left shift in the differential counts and increased total bilirubin (31·9 µmol/L, normal 3–17 µmol/L), but normal kidney function. Based on her medical history, the patient was diagnosed with mTSS, and she was given intravenous antibiotic therapy with clindamycin and vancomycin to treat possible meticillin-resistant *S aureus* (MRSA) after blood and urine cultures were taken. A nasal swab showed toxic shock syndrome toxin 1 (TSST-1)-positive *S aureus* whereas *Staphylococcus epidermidis* was detected in a vaginal swab. A urine culture done by the family doctor showed *S aureus*. MRSA genome was not detected, and antibiotic therapy with vancomycin was suspended on day 2, while intravenous clindamycin was continued.

The second course of the disease was much milder than the first, and the patient was discharged on day 4 with oral antibiotic therapy of clindamycin for a total of 14 days. A mupirocin-containing nasal cream was given to start eradication.

17 months later, the patient presented for a follow-up in good health and reported no other mTSS-like episodes. Following the advice of her gynaecologist she had stopped using tampons. Nasal and vaginal swabs at the follow-up showed no growth of *S aureus*.

Review and discussion

Todd and colleagues[1] first coined TSS in 1978, when, in a series of seven paediatric cases, they observed a new disease entity in association with phage-group-I staphylococci, which produce a new epidermal toxin that was called enterotoxin F and later renamed TSST-1.[1] Following an initial case definition and the observation of a high incidence of TSS in menstruating women in Madison, WI, USA, further studies were conducted, partly in collaboration with the CDC, to determine the pathophysiological background as well as possible disease-associated factors.[4] In 1980–81, Davis and colleagues[5] and Bergdoll and colleagues[6] established the association between mTSS and toxin-producing *S aureus* strains.[5,6]

S aureus asymptomatically colonises the skin and mucous membranes permanently in 20–50% of people and transiently in 60–70%, although it is suggested that less than 20% of the population has never been colonised.[7,8] The rate of colonisation in the vagina has been reported to be higher during menses due to the altered vaginal environment.[9] Schlievert and colleagues[10] detected an increase in frequency of isolated vaginal *S aureus* strains from 30% in 1980 to 40% in 2005. Gittelman and colleagues[11] found that up to 40% of *S aureus* had toxigenic potential.[11] Therefore, carriage ranges, and up to 40% of vaginally isolated *S aureus* strains are found to be positive for TSST-1.

Nevertheless, mTSS is rare. Parsonnet and colleagues[12] postulated that the reason for the low incidence is that most women are colonised with TSST-1-negative strains (in the nose, vagina, and anus) and appear to be protected by positive antibody titres against TSST-1. Only 24% of the women assessed by Parsonnet and colleagues exhibited co-colonisation in the nose and vagina or anus, presumably because of the unsuitable environment for the bacteria in the vagina.

Clinical criteria and symptoms

Our case met all five clinical criteria (fever, rash, desquamation, hypotension, and multi-system involvement) and the laboratory criteria of negative cultures for the diagnosis of TSS according to CDC guidelines (panel 1). 31 patients were identified from the cases compiled in the literature, of which a total of 16 patients satisfied the clinical criteria for a diagnosis of mTSS.[1,13–25] 11 patients met four of five clinical criteria and were probably mTSS cases.[16,26–29] In four patients, mTSS was

not confirmed due to an absence of erythroderma and desquamation; TSST-1-producing *S aureus* was detected in one patient out of the four (appendix).[30–33]

The symptoms of diseases caused by staphylococci are influenced by the activity of superantigens. Schlievert and colleagues[34] were able to prove that onset and severity of erythroderma depend on lymphocyte activity or superantigenicity. Moreover, many women who developed a case of mTSS meeting the CDC diagnostic criteria had already suffered at least one episode of TSS-like disease that went unrecognised due to lack of symptoms.[8] Furthermore, patients with non-mTSS who were exposed to a TSS organism only once also lacked skin changes and overall, the clinical course can be mild, without symptoms of shock.[35,36] According to the CDC criteria, these cases would not be classified as TSS and would be insufficiently treated under some circumstances, thus increasing the risk of another episode with a more serious course.

As in our patient, non-specific symptoms such as fever (30 of 31 patients), abdominal pain, nausea, vomiting and diarrhoea (20 of 31 cases), and muscle (eight of 31) and joint pain (two of 31) often appear at the very start of or during the disease, which can lead to incorrect diagnoses or serious delays (appendix).[1,13–33]

Both in the literature and in our patient, the results of the laboratory investigations show great heterogeneity. However, the severity of the disease, as measured by the organ systems involved, can be said to be reflected in the laboratory findings. In most cases, patients have increased C-reactive protein, leucocytosis, thrombocytopenia, anaemia, electrolyte shifts, and an increase in creatinine, urea, bilirubin, and liver values.[16]

In the 31 case descriptions we found in the literature, 24 of 27 blood cultures were negative for *S aureus* (blood culture results were not discussed in the other four case descriptions).[1,13–16,18–25,27,29,31,33] Lumbar punctures were all negative (11 were described in 31 cases).[1,13–16,19,29] 16 of 31 cases contained details of urine cultures, in which *S aureus* could only be detected in two of 16 patients.[17,25] The bacteria was detected twice in the nose (two of two described in 31 cases) and twice pharyngeally (two of ten described in 31 cases).[1,15,28,30] 19 of 26 vaginal and cervical swabs were positive for *S aureus*.[13,14,16–20,24–27,29–33] In five cases, the bacteria could not be detected; in two cases it was isolated from the tampon, in a third from the IUD, and in a fourth from the perineal culture (appendix).[13,16,21–23,25]

In our patient, an *S aureus* strain capable of producing TSST-1 (evidenced by presence of the gene encoding for TSST-1) was detected in the nasal smear but not in the vaginal smear. *S aureus* was found in the urine but retrospective testing of TSST-1 production in this strain was not possible due to contamination. Thus, comparison could not be made between the two *S aureus* strains. In the nasal *S aureus* isolate, several surface proteins and clumping factors were detected which facilitate colonisation of the nasal epithelium and intracellular adhesion, mediate the ability to form biofilms, and are associated with general invasiveness and virulence (appendix).

See **Online** for appendix

Epidemiology

Cotton was the primary absorbent component in tampons until the late 1970s, when manufacturers started adding synthetic superabsorbent fibres that allowed for significant TSST-1 toxin production.[37] In the 1980s, the incidence of TSS peaked in the USA at 13·7 cases per 100 000 people.[38] By 1986, following a high-profile court case, incidence rates had dropped to one to two cases per 100 000 menstruating women. Staphylococcal TSS is not a notifiable illness in Europe, and incidence is low in the USA, ranging from 0·03 to 0·5 cases per 100 000 people and seems to be stable, with overall mortality—mostly as a consequence of hypotensive shock—at around 8%.[38–41]

Pathophysiology

All pathogenic strains of *S aureus* produce superantigens, whereas TSST-1 is the only strain to cause mTSS.[4–6,8,42] These exoproteins are pyrogenic, inducing production of interleukin (IL) 1b and 6, and so function as superantigens.[43] They cause a 1×10^6 times increase in sensitivity of an organism to lethal shock triggered by Gram-negative lipopolysaccharides.[44]

TSST-1 binds to human vaginal epithelial cells (possibly via the CD40 receptor) and, in combination with cytolysins, eventually stimulates the production of pro-inflammatory chemokines, such as IL-8. This stimulation ultimately leads to the invasion of cells of the innate and acquired immune system in the submucosa and to the breakdown and permeability of the mucous membrane barriers.[45] The initial T-cell stimulation does not depend on the antigen specificity of the T-cell receptor, but on the composition of the variable part of the T-cell receptor chain (Vβ). Despite different antigen specificities, large subsets of T cells express the same Vβ region in their T-cell receptor. Superantigens activate 5–30% of all T cells, whereas a typical complex of antigen peptide MHCII stimulates host T cells at a frequency of about one in 10 000, hence 0·01%.[46]

Risk factors

In the early 1980s, clinical and epidemiological observations showed a statistically significant relationship between TSS, menstruation, and accompanying tampon use, especially continuous use during menstruation.[4,14,47] There were significant differences in tampon use between patients with TSS and control cases, with more patients using tampons every day and night throughout the menstrual period (odds ratio 9:1).[14] Our literature search confirms these observations, with 23 of 31 patients using tampons, including our patient (appendix).[13–20,22,24–33]

With incidence of mTSS increasing, and after the use of new synthetic materials in the production of tampons came to light in the late 1970s, the new tampon brand Rely (Procter & Gamble), in particular, became the focus

of public and scientific discussion. Various case–control studies showed an increased incidence of mTSS in Rely users.[48,49] However, the exact disease-promoting mechanism of tampons in combination with *S aureus* was not fully clarified at the time.

After TSST-1 was identified as a pathogen, researchers concentrated on physiochemical factors that might have led to optimal toxin production. Tierno and colleagues[50] showed that both tampons and other hygiene products create favourable chemical and physical conditions for optimal growth of *S aureus* and TSST-1 production. These include various synthetic fibre materials, which, to varying degrees, increase the viscosity and the adsorption and absorption surface area. Also, the inhibitory effects of additives like glycerol monolaurate, nonxynol-9 spermicide, and deodorants are mollified by the presence of blood or dilution.[51,52]

In-vitro studies show a promoting effect on TSST-1 production in the absence of magnesium, as an expression of the ability of absorbent tampons to bind magnesium ions.[53] The proportion of oxygen and carbon dioxide in the vaginal environment, which contains air, has a role in promoting TSST-1 production.[54–56] Likewise, α and β globin chains of haemoglobin inhibit TSST-1 production.[10] These findings were confirmed by Schlievert and Nemeth,[57] with evidence of increased TSST-1 production in areas of the tampon with low menstrual blood content. Finally, the pH and protein content also have an influence on TSST-1 production.[50] Because of their increased absorbency, highly absorbent tampons lead to longer wearing times. This results in a longer growth phase in the presence of oxygen and CO_2 upon device insertion. Increased retention time, in combination with oxygen and carbon dioxide and *S aureus,* results in increased mTSS prevalence.

As a 2018 in-vitro study[58] shows, menstrual cups are also potential risk factors, with cup shape and volume most likely to affect toxin production.

Pathogen and host mechanisms

After discovery of non-mTSS and the realisation that mTSS and non-mTSS show the same clinical picture, it soon became clear that use of intravaginal devices (tampons, diaphragms, vaginal contraceptive sponges, cervical caps, etc) cannot cause mTSS alone, but can be the initial trigger in a complex interplay of different factors. While use of vaginal protection is a critical risk factor, additional factors that may contribute include the complex interplay between pathogenicity of *S aureus,* immunological mechanisms, the immune system of the host, and changes in the vaginal ecosystem during menstruation.

Vaginal staphylococcal colonisation increases significantly during menstruation, with vaginal carriage of up to 40%.[10] Topical exposure to TSST-1 changes the permeability of the vaginal mucosa, independent of dosage, and other microbial virulence factors, such as haemolysin, increase permeability by influencing growth of *S aureus*.[59,60]

Paucity of anti-TSST-1 antibody (particularly IgG1 and IgG4), represents a risk factor for the development of mTSS.[5,12,61–64] More than half of patients with missing or low antibody titres show seroconversion within the first 2 months.[63] However, 20% of people younger than 40 years in the USA who come in with superantigens do not develop antibodies, leading to continued scientific discussion and a search for the explanation.[65] Discussion focuses on the suppression of B-cell differentiation to competent immunoglobulin-secreting cells by TSST-1, although this is not caused by direct superantigen cytotoxicity per se but by cytokines, which are secreted by the activated cells.[66] On the other hand, the influence of staphylococcal infections undergone in childhood and a relative IgG deficiency but, above all, an unbalanced serum IgG subclass pattern with low IgG2 concentrations are discussed.[67,68]

Gaventa and colleagues[37] reported teenagers to be at high risk for mTSS, assuming that antibodies against toxic *S aureus* strains only develop over the lifetime. Our literature search supports these observations: presented data show that TSST-1 antibodies of both men and women increased with age. Parsonnet and colleagues[12] rejected this claim, detecting positive anti-TSST-1 antibody titre in 81% of teenagers. However, it is not only the presence of anti-TSST-1 that is important, but also the amount of protective antibody present.[12] Thus the epidemiologically proven link between teenagers and mTSS could be due to the quantity of protective antibody against TSST-1.

In healthy women, vaginal colonisation with toxic *S aureus* strains correlates significantly with being a co-carrier of *Escherichia coli*.[69] In case reports, *E coli* was reported in the vaginal smear in addition to *S aureus* in three cases.[14,15,17] In addition, *E coli* strains have been shown to increase the growth of TSST-1-positive *S aureus* and its secretion of TSST-1.[70] This observation, as well as clinical and experimental studies, supports the hypothesis that TSST-1 has the ability to increase the human body's susceptibility to endogenous endotoxins, such as lipopolysaccharide, and that co-colonisation with *E coli* results in an increased risk of developing severe TSS.[8,71] One hypothesis is that TSST-1 seems to be able to deactivate lipopolysaccharide metabolism in the liver. Combined with a certain permeability of the gastrointestinal and vaginal mucosa to lipopolysaccharide, this deactivation leads to a synergism of the immune cell production of tumour necrosis factor (TNF)α and TNFβ. The latter causes capillary leaks.[45]

Use of hormonal contraceptives has been postulated as a protective factor against mTSS.[4,14] Low oestrogen doses of oral contraceptives cause a reduction in endometrial build-up and consequently a lower intensity and duration of menstrual bleeding. Meanwhile, progesterone has been shown to suppress the oestrogen-induced growth of

vaginal bacterial colonisation in rats, leaving combined oral contraceptives to be discussed as a protective factor, possibly requiring further analysis.[72] Our patient was regularly taking an oral contraceptive containing ethinylestradiol and cyproterone acetate. This may be one reason why the course of symptomatic mTSS in our patient was milder than in other cases described previously.

The development of recurrent infections has been observed for mTSS in particular, with a rate of up to 28%, although the recurrence was often milder, as in our patient.[4,47] Six (9·3%) of 31 previous case reports in the literature involved recurrent infections, with more than one repeat infection occurring in two of those cases (appendix).[13,15,17,18,22,28] This could be due to continued use of tampons after an mTSS episode, as well as insufficient antibody formation against TSST-1.[18,22,28] β-lactam-resistant antibiotic therapies may also lead to a reduced rate of reinfection.[73] Protective factors and risks are summarised in panel 2.

Therapy

Ensuring rapid and efficient treatment once there is a suspicion of mTSS is crucial, and the threat of multi-organ failure necessitates treatment in a hospital with the appropriate intensive care resources.

An essential first step in the treatment of mTSS is the removal of any potential intravaginal or intrauterine device and the elimination of other obvious focal points of infection, such as abscesses. This requires a thorough physical examination and possibly also MRI or CT.[2]

Microbiological cultures of tampons or intravaginal devices and of blood and urine, a vaginal smear, and an additional cervical smear when endometritis is suspected, as well as swabs of other suspicious parts of the body or bodily fluids, should be standard.

A key focus is the supportive treatment of hypotension. Depending on severity, patients may need intensive medical treatment for complications such as acute kidney failure, acute respiratory distress syndrome, and disseminated intravascular coagulation. In addition, especially since sepsis often cannot be ruled out clinically in the early phase of the disease, empirical antibiotic therapy should start as soon as possible, ideally after removal of all microbiological materials relevant for further diagnosis.

Clindamycin is the first choice for treatment if mTSS is confirmed. Clindamycin demonstrably reduces the production of superantigens, both directly and indirectly, by inhibiting the transcription of exoprotein genes, which interrupts the stimulation of the inflammation cascade.[2,74–76] Even a sublethal concentration of clindamycin stops TSST-1 toxin production.

Most mTSS cases around the world are induced by meticillin-sensitive *S aureus* strains, so that in addition to an antitoxin therapy with clindamycin, antibacterial therapy with cloxacillin is recommended. Because of the widely ranging MRSA prevalence worldwide, empirical therapy with vancomycin is only recommended if there is high suspicion of an MRSA strain.[4,73] Linezolid has been successfully used in the treatment of non-mTSS cases and has also been shown to reduce TSST-1 production.[77]

The administration of intravenous immunoglobulins has been discussed for patients with insufficient immune

***Panel 2*: Overview of factors influencing menstrual toxic shock syndrome**

Protective factors

- Oral contraceptives[4,14,55,72]
- DRB1*1501/DQB1*0602 MHCII haplotypes[82,83]

Risk factors

- Colonisation with toxic shock syndrome toxin-1-positive *Staphylococcus aureus*[1,5,6,14,81]
- Use of tampons or other vaginal devices[4,14,47,50,57,84,85]
- Deep or insufficient toxic shock syndrome toxin antibodies, especially of the sub-classes IgG1 and IgG4[12,61,62,64,67,86–88]
- Gram-negative co-colonisation[8,34,45,70,71,89]

***Panel 3*: Diagnostic algorithm and management of mTSS**

Early detection, "Be aware of it"

- History: US Centers for Disease Control and Prevention criteria, temporal association with menstruation, women of reproductive age

Finding and removing the source of infection

- Extensive physical examination and, if necessary, imaging
- Elimination of intravaginal/intrauterine devices or other focal points of infection

Laboratory and microbiological diagnostics

- Microbiological tests (blood and urine cultures, vaginal and nasal smears)

Supportive therapy

- Fluid management, maintenance of organ function, ventilation and, if necessary, early intensive care measures

Empirical antibiotic therapy

- Intravenous clindamycin (adults 900 mg intravenous every 8 h) plus intravenous oxacillin or nafcillin (2 g every 4 hours)

Adjustment of antibiotic therapy in line with test results and in cases of a high or confirmed suspicion of mTSS

- Meticillin-susceptible *Staphylococcus aureus*: intravenous clindamycin (adults, 900 mg every 8 h) plus intravenous oxacillin of nafcillin (2 g every 4 hours)
- Meticillin-resistant *S aureus*: intravenous clindamycin (adults, 900 mg every 8 h) plus intravenous vancomycin (adults, 15–20 mg/kg every 8–12 h, not to exceed 2 g per dose) or oral or intravenous linezolid alone (adults, 600 mg every 12 h) or in combination with vancomycin

Further treatment options

- Intravenous immunoglobulins if patient is immunoincompetent

Minimise the risk of recurrent infection

- Prophylaxis (eg, no vaginal devices)
- Eradication: mupirocin if a nasal carrier of *S aureus*
- Re-evaluation of patients for risk stratification

mTSS=menstrual toxic shock syndrome.

Search strategy and selection criteria

PubMed was searched and the search was updated through Dec 10, 2018, using the key words "toxic shock syndrome" in combination with "menstrual, tampon, risk factors, antibodies, *Staphylococcus aureus*, host, hygiene, interleukin, superantigens" and related terms. Further studies were found by screening the references of papers that covered the topics. The search yielded 22 relevant publications with 31 case reports (appendix). We included studies and cases published between 1978 and 2018.

We concentrated on female patients with menstruation-associated toxic shock syndrome caused by *S aureus*. Additional inclusion criteria were menstrual association of symptoms listed in the US Centers for Disease Control and Prevention (CDC) criteria, historical association with menstrual toxic shock syndrome, evidence of *S aureus*, and patient use of vaginal products. Not all four conditions had to be fulfilled at the same time. Case reports were excluded if there was no menstrual association of the symptoms or no vaginal protection of any form. The following end points were compared: year of case, epidemiological findings, symptoms and onset of illness, fulfilment of the CDC's criteria, laboratory findings, antibiotic treatment, recurrence, and risk factors. A few case collections were not included in the appendix because of partly incomplete patient data, but were taken into account in the discussion.

response; the anti-inflammatory and immune-modulatory effect of intravenous immunoglobulins could improve outcome.[2] So far, there is no definitive evidence from randomised controlled studies, but some observational studies exist.[78]

The administration of corticosteroids is not recommended since there are few clinical data. Panel 3 gives an overview of a proposed diagnostic algorithm for the management of mTSS.

Conclusion

mTSS remains a clinical diagnosis, with a risk of misdiagnosis or delayed diagnosis due to its rarity and initially non-specific symptoms or even mild course of the disease. Doctors should therefore be aware and mindful of the disease when dealing with corresponding risk groups, followed by thorough gynaecological history-taking. The CDC criteria can aid in diagnosis and are certainly important for epidemiological observations, but they have appreciable limitations in everyday clinical practice.

Given the limitations of the criteria, it is not sensible to rigidly adhere to them to rule out TSS; stringent adherence in the past may have led to under-reporting, which eventually resulted in the apparently low prevalence of the disease. In the acute phase of the disease, often not all diagnostic criteria are met. Furthermore, some criteria can only be confirmed or ruled out retrospectively. Too much emphasis on the CDC criteria could therefore lead to delayed or even inadequate therapy. Moreover, a strict time limit does not make sense from our point of view. The diagnosis of mTSS should always be considered when there is a certain temporal relationship between the onset of the disease and menstruation.

In addition to early removal of any potential intravaginal devices and supportive intensive care measures, therapy should include the administration of clindamycin, as this antibiotic interferes with protein synthesis and therefore TSST-1, which is an exoprotein. Linezolid is an alternative. Our literature search indicated that mTSS caused by MRSA is very rare. However, two cases were reported in 2017, so that empirical therapy with vancomycin should be initiated only if an MRSA strain is highly suspected, mostly based on the epidemiological rate of MRSA. In cases of inadequate response, complementary intravenous immunoglobulin therapy should be considered.

In addition to informing patients that they should never use tampons again after a case of mTSS, we believe it makes sense to re-examine the patient in a follow-up consultation. This should be done for the purposes of risk stratification for further infection, and includes nasal and vaginal screening for TSST-1-producing *S aureus* after initial antibiotic treatment has been completed (nasal and vaginal), as well as TSST-1 antibody detection.

At least 18–25% of *S aureus* harbour a gene encoding TSST-1.[79,80] Schlievert and colleagues[10] detected an increase in frequency from 30% in 1980 to 40% in 2005 in isolated vaginal *S aureus* strains.

We believe that further diagnostic testing and clarification procedures are not indicated. Available data are insufficient with regard to the influence of hormone status. Furthermore, in terms of cost versus benefit, the determination of antibody sub-classes or haplotype typing must be critically scrutinised, especially in view of the low incidence of the disease and other, more cost-effective prophylaxis options (such as not using feminine hygiene products).

We see the time delay between the onset of symptoms and a reliable diagnosis as problematic. On the one hand, this is due to late clinical confirmation by desquamation in the convalescence phase. On the other hand, microbiological detection of a TSST-1-positive *S aureus* strain in the swab, by means of cultivation, takes at least 2–3 days on average. Furthermore, many *S aureus* contain a gene encoding TSST-1. The use of molecular testing for TSST-1 detection will overestimate the diagnosis of TSS. Molecular tests can only confirm the presence of the TSST-1 gene, reinforcing the diagnosis of TSS in a defined clinical context.

Other diagnostic methods, such as antibody-based, RT-PCR-based, or aptamer-based methods, would also be a possibility for faster diagnostics. However, these testing techniques are considerably more expensive or not available everywhere.

Initial efforts to develop a staphylococcal vaccine targeting capsular polysaccharides, as for other bacterial pathogens, were not successful. The development of a vaccine against *S aureus* remains of interest, not the least due to the global threat from antibiotic-resistant *S aureus* strains. Women who lack a protective antibody to TSST-1 and who use feminine hygiene products seem to be at greatest risk for TSS development. Clearly, as evidenced by our case report, mTSS is still first and foremost a clinical diagnosis, and recognising or even preventing it requires that physicians in hospitals, general practitioners, and menstruating women are educated about the potential risks of feminine hygiene products.

Contributors

SB, AK, SW and JB were the patient's internal medicine physicians. SB, AK and JB wrote the initial draft, did the review of the literature and edited the manuscript. SW, KW and PT reviewed and edited the manuscript. KW did the whole genome sequencing together with Peter Keller and wrote these sections of the text.

Declaration of interests

The authors declare no competing interests.

Acknowledgments

Medical editor Jeannie Wurz of Bern edited the final version of the manuscript. We thank Peter Keller for fruitful input and whole genome sequencing of the nasal strain.

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