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ARTICLE

One in five mortality in non-menstrual toxic shock syndrome versus no mortality in menstrual cases in a balanced French series of 55 cases

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Abstract *Staphylococcus aureus* superantigenic toxins are responsible for menstrual and non-menstrual toxic shock syndrome (TSS). We compared the clinical and biological characteristics of 21 cases of menstrual TSS (MTSS) with 34 cases of non-menstrual TSS (NMTSS) diagnosed in France from December 2003 to June 2006. All 55 *S. aureus* isolates had been spontaneously referred to the French National Staphylococcal Reference Center, where they were screened for superantigenic toxin gene sequences. Most of the patients had previously been in good health. The most striking differences between MTSS and NMTSS were the higher frequency in NMTSS of neurological disorders (p=0.028), of *S. aureus* isolation by blood culture (50% versus 0% in MTSS), and the higher mortality rate in NMTSS (22% versus 0% in MTSS). The *tst* and *sea* genes were less frequent in isolates causing NMTSS than in those causing MTSS (p<0.001 and 0.051, respectively). Higher mortality was significantly associated with the presence of the *sed* gene (p=0.041), but when considering NMTSS survivors and non-survivors, no clinical or bacteriological factors predictive of vital outcome were identified. Specific antitoxinic therapy was rarely prescribed, and never in fatal cases. Higher mortality was observed in NMTSS than in MTSS, and no definite factors could explain the higher severity of NMTSS. NMTSS would require more aggressive therapy, comprising systematic rapid wound debridement, antistaphylococcal agents, including an antitoxin antibiotics, and intravenous immunoglobulin.

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Introduction

Staphylococcus aureus causes a variety of infectious diseases, ranging from superficial skin infections to severe, toxin-mediated systemic infections [1, 2]. Toxic shock syndrome (TSS) has been linked to toxic shock syndrome toxin-1 (TSST-1) and also to staphylococcal enterotoxins (SE), such as SEB, SEC, and, to a lesser extent, SEA and SED [3, 4]. All of these staphylococcal toxins act as superantigens, leading to the massive release of proinflammatory cytokines, which are thought to be responsible for the clinical manifestations of TSS [3, 5, 6].

TSS is characterized by the sudden onset of fever, cutaneous signs (rash followed by desquamation), hypotension, and multisystem involvement [6, 7]. It is fatal in less than 5% of cases [8]. Most reported cases correspond to menstrual TSS (MTSS) and involve young, healthy menstruating women, especially those using tampons [9].

TSS can also occur without relation to menstruation, such as that initially described in children with *S. aureus* mucosal colonization or focal infection [10]. Unlike patients with MTSS, patients with non-menstrual TSS (NMTSS) form a heterogeneous group with a wide age range, various comorbidities, and different sites and types of *S. aureus* infection [11]. While the incidence of MTSS fell after changes were made to tampon absorbency and chemical composition, the frequency of NMTSS seems to have remained stable since 1985 [4, 8, 12].

Each year, the French National Staphylococcal Reference Center collects about 40 *S. aureus* strains recovered from patients with suspected TSS throughout France. The objective of this study was to compare the bio-clinical characteristics and outcomes of MTSS and NMTSS.

Materials and methods

Collected data

We prospectively collected cases of suspected staphylococcal TSS diagnosed in France between December 2003 and June 2006. All of the corresponding *S. aureus* isolates were spontaneously referred by hospitals or private laboratories to the French National Staphylococcal Reference Center for toxin detection. Information was collected on a standard form completed by the referring clinician or biologist, together with medical files and telephone contact with the referring clinicians.

TSS was defined according to the Centers for Disease Control and Prevention (CDC) diagnostic criteria (http://www.cdc.gov/epo/dphsi/casedef/toxicsscurrent.htm). Both confirmed and probable cases of TSS were included. A case of TSS was considered menstrual if symptoms onset occurred within three days of the beginning or the end of menses; all other cases were considered as non-menstrual [8].

The following data were recorded in each case: age, sex, comorbidity, clinical manifestations included in the CDC case definition of TSS, the depth and location of the primary focal infection, tampon use in MTSS, community or nosocomial origin, and postoperative occurrence. Biological data included the results of blood culture, the methicillin sensitivity, and the toxin gene profile of isolates. Information on treatment and outcome was also collected.

Microbiological studies

All *S. aureus* isolates were tested for toxin production at the French National Staphylococcal Reference Center. Gene sequences encoding superantigenic toxins (TSST-1, SEA, SEB, SEC, SED, SEH, SEK, SEL, SEM, and SEO) were detected by using polymerase chain reaction (PCR)-based methods [13]. The *mec*A gene coding for methicillin resistance was also detected by PCR [14].

Statistical analysis

All data were analyzed with SPSS software version 12.0 (SPSS Inc., Chicago, IL). Descriptive statistics were reported as means, standard deviation (SD), and medians for quantitative variables, and as frequencies and percentages for qualitative variables. We first compared MTSS and NMTSS cases, and then survivors and non-survivors of TSS and NMTSS. The log rank test was used to compare the age distributions of the patients between the two groups. Fisher's exact test was used to compare all other variables. p values below 0.05 were considered to indicate statistical significance.

Results

Among 100 patients with suspected staphylococcal TSS diagnosed in France from December 2003 to June 2006, 55 patients met the CDC case definition for confirmed (20 cases) or probable TSS (35 cases). The cases originated throughout France, and there was no seasonal or epidemic pattern (mean, 1.77±1.36 cases per month; median, 1 case per month; range, 0 to 5 cases per month). There were 21 cases of MTSS (38%) and 34 cases of NMTSS (62%).

The demographic, clinical and biological characteristics, and outcome of these 55 patients are summarized in Table 1. None of the patients with MTSS and only 29% of the patients with NMTSS had comorbidities, confirming that TSS mainly occurs in otherwise healthy subjects. Tampon use was reported in 19/21 cases of MTSS (90%). Female patients predominated in the NMTSS group (62%). Patients with NMTSS were older than patients with MTSS (log rank, p=0.008) and were significantly more likely to have comorbidities (p=0.039). Information on desquamation was often unavailable because of death or early discharge. Patients with MTSS were more likely than patients with NMTSS to have digestive symptoms and mucosal hyperemia (p=0.009 and 0.024, respectively). Neurological disorders were more frequent in patients with NMTSS (p=0.028). Eight of the 34 cases of NMTSS (24%) occurred in hospital. NMTSS was postoperative in 7/34 cases (21%), occurring after slipped-disc surgery (three cases), inguinal hernia surgery, hip replacement, heart surgery, and breast cancer excision (one case each). Blood culture yielded *S. aureus* in 17 cases of NMTSS (50%) and in no cases of MTSS (p<0.001). Methicillin resistance was only detected among NMTSS isolates (12%, four community-acquired cases). Genes encoding staphylococcal superantigens were screened for in all 55 *S. aureus* isolates. The *tst* gene

Table 1 Demographic, clinical and biological characteristics, and vital outcome of 55 patients with toxic shock syndrome (TSS)

	Menstrual TSS, *n*=21 (%)	Non-menstrual TSS, *n*=34 (%)	*p*[a]
Age in years mean±SD	20.7±8.7	32.4±24.9	
median	19	33	
range	10–47	0–84[b]	0.008
Sex ratio F/M	21/0	21/13	
Comorbidity	1/20 (5)	10/34 (29)	0.039
CDC diagnostic criteria			
confirmed cases	8/21 (38)	12/34 (35)	NS
probable cases	13/21 (62)	22/34 (65)	NS
1. fever	21/21 (100)	33/34 (97)	NS
2. rash	21/21 (100)	32/33 (97)	NS
3. desquamation	10/13 (77)	14/20 (70)	NS
4. hypotension	19/21 (90)	33/34 (97)	NS
5. ≥3/7 organ involvement	21/21 (100)	32/33 (97)	NS
digestive	21/21 (100)	25/34 (74)	0.009
muscular	15/21 (71)	19/34 (56)	NS
mucosal	16/21 (76)	14/33 (42)	0.024
renal	17/21 (81)	23/33 (70)	NS
hepatic	8/21 (38)	21/33 (64)	NS
hematologic	11/21 (52)	25/33 (76)	NS
neurologic	6/21 (29)	20/33 (61)	0.028
Methicillin-resistant *S. aureus*	0/21 (0)	4/34 (12)	NS
S. aureus positive blood culture	0/21 (0)	17/34 (50)	<0.001
S. aureus toxin gene profile			
tst	20/21 (95) [c]	16/34 (47)	<0.001
sea	15/21 (71) [d]	14/34 (41)	0.051
seb	0/21 (0)	2/34 (6)	NS
sec	1/21 (5)	9/34 (26)	NS
sed	1/21 (5)	6/34 (18)	NS
she	2/21 (10)	3/34 (9)	NS
sek	0/21 (0)	3/34 (9)	NS
sel	1/21 (5)	9/34 (26)	NS
sem	19/21 (90)	21/34 (62)	0.029
seo	19/21 (90)	21/34 (62)	0.029
Mortality	0/21 (0)	7/32 (22)	0.034

[a] *p* values are for MTSS vs NMTSS (Fisher's exact or log rank tests)
[b] One patient developed TSS on his first day of life, after maternofetal transmission
[c] In one *tst*-negative probable case of MTSS associated with thigh cellulitis, *sec*, *sel*, *sem*, and *seo* were detected
[d] All of these *sea*-positive strains were *tst*-positive

(encoding TSST-1) was detected in 20/21 MTSS isolates (95%) and in 16/34 NMTSS isolates (47%) ($p<0.001$). The *sea* gene was also more frequent in MTSS isolates ($p=0.051$). Both genes (*tst* and *sea*) were detected in 15/21 MTSS isolates (71%) and in 10/34 NMTSS isolates (30%). The *egc* locus, harboring the *sem* and *seo* genes, was more frequent in MTSS isolates than in NMTSS isolates ($p=0.029$). Genes encoding others staphylococcal enterotoxins (e.g., *seb*, *sec*, or *sed*) were more frequent in NMTSS than in MTSS, but the difference was not statistically significant. No superantigenic toxin genes were detected in one isolate (from a patient with probable TSS). Higher lethality was significantly associated with the presence of the *sed* gene ($p=0.041$), but no significant correlation was detected between the toxin gene profile and neurological symptoms or positive blood culture (Tables 2 and 3).

Most of the primary focal *S. aureus* infections in NMTSS patients were trivial. For instance, a 26-year-old man developed signs of TSS 36 hours after inguinal hernia surgery; the surgical scar showed no signs of inflammation or infection, but a slight serous exudate that yielded *S. aureus* in culture was found on reopening the wound 3 days after initial surgery. Four patients (12%) had *S. aureus* bacteremia of unknown origin, whereas the others had focal or various other infections. The focal infections were usually superficial and involved the skin or mucosa (22/34 cases, 65%), while the remainder were deep-seated [bones or joints, three cases (9%); lung or heart, two cases each (6%); gall bladder, one case (3%)].

The outcome was known for all patients with MTSS and for 32 of the 34 patients with NMTSS. Seven patients with NMTSS died (22%) rapidly after symptom onset (median, 3 days; range, 1–17 days, Table 4). Two of these cases were post-operative. Patients who died had been treated more aggressively than survivors (more frequent vasopressive therapy and mechanical ventilation), but none had received clindamycin, linezolid, or intravenous immunoglobulin (IVIg). When comparing the group

Table 2 Correlation between staphylococcal toxin genes and neurological manifestations or *Staphylococcus aureus* bacteremia or outcome in 55 patients with TSS

	Staphylococcal toxin genes detected									
	tst	*sea*	*seb*	*sec*	*sed*	*seh*	*sek*	*sel*	*sem*, *seo*	p^a
All TSS cases, *n*=55	36	29	2	10	7	5	3	10	40	
(%)	(65)	(53)	(4)	(18)	(13)	(9)	(5)	(18)	(73)	
Neurological involvement, *n*=26	15	14	1	6	2	4	3	6	18	NS
(%)	(58)	(54)	(4)	(23)	(8)	(15)	(12)	(23)	(69)	
S. aureus bacteremia, *n*=17	6	5	2	5	5	2	2	5	10	NS
(%)	(35)	(29)	(12)	(29)	(29)	(12)	(12)	(29)	(59)	

[a] Significant association with Fisher's exact test ($p<0.05$)

of non-survivors with that of all survivors, there was no correlation between death and gender (p=0.55), the presence of comorbidities (p=0.15), positive blood cultures (p=0.18), neurological involvement (p=0.38), intestine/mucosal involvement (p=0.68), or hepatic involvement (p=0.10). In contrast, there was a significant correlation between death and the presence of the *sed* gene (p=0.041), but not between death and the absence of *tst* and *sea* gene detection (p=1 and 0.69, respectively). The significant association between the presence of the *sed* gene and death was not found when the analysis was restricted to the NMTSS group (Table 3). No other significant correlation was made between death and the presence of the other toxin genes (Table 3). Methicillin resistance was not associated with outcome (it was detected in one of the seven strains in the NMTSS non-survivors and in three of the 25 isolates in the NMTSS survivors).

Discussion

S. aureus could be responsible for menstrual and non-menstrual TSS. To compare their clinical and biological characteristics, we have collected over a 30-month period 21 cases of MTSS and 34 cases of NMTSS. MTSS continues to occur in France, as well as elsewhere, despite the less frequent use of high-absorbency tampons and changes in tampon chemical composition, albeit infrequently [4]. Menstrual cases, by definition, affect young women. It is noteworthy that females also predominated in the NMTSS group (62%). NMTSS tended to affect young subjects (median, 33 years), but the patients' ages ranged from 0 to 84 years in this series.

In a review of 130 cases of NMTSS, Reingold et al. [15] reported that TSS can result from innocuous or unapparent cutaneous *S. aureus* infections. Likewise, Bartlett et al. [16] described 13 cases of postoperative NMTSS, among which, focal signs of surgical wound infection were minimal or absent in 11 cases. This may be explained by the fact that most strains causing TSS produce very small quantities of most exoproteins, but large amounts of toxins such as TSST-1 [17, 18]. In vivo, these strains can cause local infections that are remarkably apurulent, but potentially fatal, owing to their superantigen expression [11, 15, 16, 18, 19]. It is, therefore, crucial for all physicians to be aware of the possibility of occult focal infections in patients with symptoms of TSS, particularly in the postoperative period.

Table 3 Toxin gene usage and vital outcome of patients with TSS and non-menstrual TSS (NMTSS)

	All cases of TSS, *n*=53[a]			NMTSS cases, *n*=32[a]		
	Survivors, *n*=46 (%)	Non-survivors, *n*=7 (%)	p^b	Survivors, *n*=25 (%)	Non-survivors, *n*=7 (%)	p^b
S. aureus toxin gene						
tst	30 (65)	5 (71)	NS	10 (40)	5 (71)	NS
sea	25 (71)	3 (41)	NS	10 (40)	3 (43)	NS
seb	2 (4)	0 (0)	NS	2 (8)	0 (0)	NS
sec	8 (17)	2 (29)	NS	7 (28)	2 (29)	NS
sed	4 (9)	3 (43)	0.041	3 (12)	3 (43)	NS
seh	4 (9)	1 (14)	NS	2 (8)	1 (14)	NS
sek	3 (6)	0 (0)	NS	3 (12)	0 (0)	NS
sel	8 (17)	2 (29)	NS	7 (28)	2 (29)	NS
sem	34 (73)	5 (71)	NS	15 (60)	5 (71)	NS
seo	34 (73)	5 (71)	NS	15 (60)	5 (71)	NS

[a] The outcome was not recorded for two patients with NMTSS

[b] p values are for survivors vs non-survivors and significant association with Fisher's exact test <0.05

Table 4 Description of the seven fatal cases of NMTSS

Sex/age (in years)	Comorbidity	*S. aureus* infection before TSS	Hospital origin	Neurological involvement	*S. aureus* blood cultures	*S. aureus* toxin gene	Day of death[a]
M/52	hypertension	pneumonia	no	no	positive	*sed*	D3
F/41	no	sciatica on NSAIDs 24 h before TSS onset	no	yes	positive	*tst*, *sec*, *seh*, *sel*, *sem*, *seo*	D4
F/42	no	non-suppurative surgical wound	yes slipped-disc surgery 3 days before TSS onset	yes	negative	*tst*, *sea*, *sem*, *seo*	D2
F/9	immunosuppressive treatment for renal transplantation	toe inflammation	no	yes	negative	*tst*, *sem*, *seo*	D14
F/4	congenital cardiac malformation (IVC)	suppurative surgical wound and mediastinitis	yes cardiac surgery (IVC) 7 days before TSS onset	yes	positive	*sea*, *sed*	D17
F/14	no	burns 3 days before TSS onset	no	no	negative	*tst*, *sea*, *sem*, *seo*	D0
M/59	no	shoulder arthritis on NSAIDs 3 days before TSS onset	no	yes	positive	*tst*, *sec*, *sed*, *sel*, *sem*, *seo*	D3

NSAIDs=non-steroidal antiinflammatory drugs; IVC=interventricular communication
[a] D0 indicates the day of onset of TSS symptoms

Different characteristics between MTSS and NMTSS were observed. In NMTSS, blood culture was frequently positive with *S. aureus* (50%), but not in MTSS (0%). Additionally, neurological disorders were significantly more frequent in NMTSS than in MTSS, as previously reported by Kain et al. [11]. We recently showed that TSST-1 can affect the brain, by inducing both an intracerebral increase in PGE2 and direct caspase-dependent neuronal death [20]. A higher frequency of neurological disorders in NMTSS might be explained by a higher pro-inflammatory response during NMTSS, which combines sepsis and toxemia. It could be also due to the differences in toxins involved in NMTSS and MTSS because we observed a heterogeneous distribution of toxins between the two forms. The *tst* (encoding TSST-1) and *sea* genes were more frequent in MTSS isolates than in NMTSS isolates (95% versus 47% and 71% versus 41%, respectively), as also observed by Kain et al. [11]. We recently showed that inflammatory properties of staphylococcal superantigens differ from each other [21]. Non-TSST-1 and non-SEA staphylococcal superantigens (e.g., SEB, SEC, and SED) may be more neurotoxic.

The most striking difference between MTSS and NMTSS was the higher mortality rate associated with NMTSS (22%), whereas no death occurred among patients with MTSS. The overall case/fatality ratio in our study is higher than that reported elsewhere. In 1982, Reingold et al. [15] reported 12 deaths (9.2%) among 130 patients with NMTSS. Between 1987 and 1996, the overall case/fatality ratio in the United States was 4.1% (3% for MTSS and 5% for NMTSS), and was significantly higher in NMTSS [8]. In 1993, Kain et al. [11] also reported higher morbidity and mortality associated with NMTSS (12.5% mortality versus 4.8% in MTSS). We were not able to recognize any factor predictive for mortality in the NMTSS patient group when comparing toxin gene content, organ involvement, *S. aureus* bacteremia, and methicillin resistance. In our series, NMTSS and MTSS *S. aureus* isolates presented different patterns of toxin production. Despite the fact that the *S. aureus* toxin gene profiles of fatal cases were all different, there was a significant association between the presence of the *sed* gene and death (p=0.041). However, comparing NMTSS survivors and NMTSS non-survivors, this association was not significant. To our knowledge, the severity of SED-related infections has never been specifically studied.

The passive method of TSS case recruitment used in this study may have influenced our findings. Indeed, given the lack of active surveillance in France, it is likely that only more severe cases of both MTSS and NMTSS were reported to the French National Staphylococcal Reference Center. Hence, the mortality rate may be higher than in the general population of patients with TSS. However, it does not explain the differences of fatality observed between the two groups. This is the first estimate of the mortality rate of TSS in Europe, as all of the other published data originate from the United States [8, 15] or Canada [11]. Alternatively, this high mortality rate of NMTSS could reflect increasing *S. aureus* virulence. *S. aureus* blood culture was positive in 50% of our NMTSS cases and in 0% of MTSS cases. Bacteremia could partially

explain the severity of NMTSS as stated for neurological symptoms, possibly via a combination of superantigenic toxins and *S. aureus* pyogenicity. Bacterial proliferation jointed with toxin release might provoke a composite form of shock, borderline between septic shock and TSS, potentially more severe than TSS itself [22]. We found no predictors of vital outcome among patients with NMTSS, although treatment was more aggressive in fatal cases owing to the greater clinical severity. Antistaphylococcal agents (β-lactamase-resistant antibiotics) are recommended to eradicate the focus of toxin-producing staphylococci, to treat or prevent bacteremia, and to significantly reduce the recurrence rate [7, 23]. Moreover, as in NMTSS, the toxins are released from a focal site of infection and surgical debridement may be warranted. Clindamycin and linezolid could be used to inhibit toxin production [24, 25], as they reduce TSST-1 synthesis [26]. Patients who develop TSS have little or no immunity to TSST-1 or enterotoxins. Experimental studies have shown that antibodies which neutralize TSST-1 are clinically effective [27, 28]. IVIg contains neutralizing antibodies against staphylococcal virulence factors, including toxins such as TSST-1 [29, 30]. It is speculated that the routine administration of antitoxinic antibiotics and IVIg to patients with TSS could improve their outcome, as it does for streptococcal TSS [3, 31–33]. Surprisingly, these specific antitoxinic treatments have rarely been prescribed in our series, and never to patients who died.

Conclusion

In conclusion, the most striking finding of this study is the high mortality rate of non-menstrual toxic shock syndrome (NMTSS) (22%) compared to menstrual toxic shock syndrome (MTSS) (0%). No definite factors, despite the more frequent detection of the *sed* gene in the non-survivors, could explain the higher severity of NMTSS. More adapted treatment, including rapid wound debridement (whatever the degree of local inflammation); the early administration of antistaphylococcal agents, including an antitoxinic antibiotic, such as clindamycin or linezolid; and IVIg administration could improve the vital prognosis of patients with NMTSS.

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