Enterotoxins and toxic-shock syndrome toxin-1 in non-enteric staphylococcal disease

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SUMMARY

Over the 7 years 1985–91, 997 strains of *Staphylococcus aureus* from 962 patients with diseases other than food poisoning have been tested for the production of enterotoxins and toxic shock syndrome toxin-1 (TSST-1) and phage typed. In all, 128 cases could be classified as confirmed or probable toxic shock syndrome (TSS) but a further 199 cases were classified as possible or unconfirmed TSS. In 219 cases, an alternative diagnosis could be supported and 45 cases were classified as sudden infant death syndrome. In 371 cases, insufficient information for classification was available.

Strains of phage group I producing TSST-1 were associated with menstrual TSS. Many menstrual TSS cases were aged less than 20 and were using non-introducer tampons.

When all strains were reviewed, strong associations were observed between TSST-1 production and phage group I strains, enterotoxin B production and group V strains, enterotoxin C and phage-type 95 strains and between enterotoxin A without TSST-1 and phage group III strains.

INTRODUCTION

Staphylococcus aureus may produce a variety of extracellular substances including the enterotoxins SEA-SEE, toxic shock syndrome toxin-1 (TSST-1), exfoliative toxins ETA and ETB besides the classical haemolysins, leucocidins and other exoenzymes, which may themselves be intrinsically toxic. This paper addresses the sources, strains and clinical effects of the enterotoxins and TSST-1 in patients not considered to be part of an incident of food poisoning but in whom toxic effects were suspected.

Food poisoning results from the ingestion of preformed enterotoxin in food and results in a dramatic but relatively short-lived syndrome characterised by vomiting and diarrhoea. The characters of strains of *S. aureus* from food poisoning have been studied separately (Wieneke and colleagues in preparation).

The staphylococcal scalded skin syndrome (SSSS) is related to exfoliative toxin production, usually affects infants, characteristically by blistering, and is related to group II strains though exfoliative toxins may be produced by other phage

groups. These syndromes are not further discussed though a question of misdiagnosis in some cases may be justified.

The occurrence of many cases of septic shock with a morbilliform rash, desquamation and multiple organ system failure related to a particular tampon used by young menstruating females in the United States [1] led finally to the recognition that a new toxin, TSST-1, sometimes known as SEF [2] or pyrogenic exotoxin C [3] was involved. The syndrome had already been recognized [4] but strict criteria were not established until the outbreak. Although the outbreak appeared to be associated with menstruation, non-menstrual TSS was accepted [5].

The role of enterotoxin B in lethal staphylococcal disease had been recognized for some time. Hallander and Laurell [6] found an excess of SEB producing strains in post mortem material. Schlievert [7] showed that SEB could be related to non-menstrual toxic shock syndrome and we demonstrated that Group V strains could be the source of this toxin [8, 9]. Recently, German workers confirmed that the SEB producers in post-mortem specimens type with group V [10].

An even wider significance of enterotoxins in non-food poisoning disease has been postulated by Arbuthnott and his colleagues [11, 12] who have shown that enterotoxin production and TSST-1 production are more frequent than expected in septicaemia cases as compared with strains from healthy carriers. Burns may also be a situation in which toxic effects are significant [13] though not all reach the diagnosis of confirmed toxic shock.

In order to document the incidence of TSS in the UK and to investigate the importance of toxin production in other syndromes, a questionnaire was included with the phage-typing report whenever a strain of *S. aureus* was received with a request for toxin testing [14]. While the primary aim was to monitor the frequency of TSS, many referrals were made because toxic effects could have contributed to a clinical picture that was not primarily TSS. We review the results of the last 7 years because the availability of toxin testing kits mean that CPHL is no longer the only source of toxin production testing in the UK.

METHODS

Microbiological methods

From 1985 to the end of 1991 the Staphylococcus Reference Laboratory received 997 isolates of *S. aureus* from 962 patients believed to be suffering from staphylococcal disease other than food poisoning in which toxins might be significant. Each isolate was typed by standard methods [15] with the 23 International phages at routine test dilution (RTD) and at RTD $\times$ 100 and allocated to the standard phage groups [16]. In addition four experimental phages, 88A, 90,83C and 932, were included at RTD $\times$ 100. Isolates typing only with these phages formed the 'Experimental' phage group. Antibiotic resistance to penicillin, tetracycline, erythromycin, fusidic acid, kanamycin, gentamicin and methicillin was assessed by a standard disk method [17].

Each isolate was transferred to the Food Hygiene Laboratory where tests for production of enterotoxins A-E and TSST-1 were performed using the double gel diffusion technique [18]. Exfoliative toxins were not sought.

Clinical classification

Clinical details were available from the referral letter and from the responses to the questionnaire sent out with the phage typing report. Additional information was often proffered but there was no active follow-up where data were missing.

Patients were classified on the available information using the revised CDC Atlanta criteria [5] which permit staphylococcal bacteraemia, into:

1. Confirmed TSS all criteria satisfied.
2. Probable TSS one criterion missing or not recorded.
3. Possible TSS two criteria missing or not recorded.
4. Unconfirmed three criteria missing or not recorded.
5. Not TSS an alternative diagnosis seemed appropriate.
6. No data insufficient data was available to classify.
7. SIDS sudden infant death syndrome.

In the first five groups and to a degree in the last group, data was available but in group 6 the referral letter might state only 'Clinical TSS' and the questionnaire was not returned. This group undoubtedly includes true cases of toxic shock but these cannot be validated. The distinction between septic shock and toxic shock in fatal cases often depended on the recording and description of the rash alone.

Because TSS is defined strictly on clinical criteria, lesser expressions of the same disease that are clearly the same process cannot be included in the confirmed and probable TSS groups. Comparison of the possible TSS group with the first two groups may support this view and differences between these groups and group 5 where an alternative diagnosis was deemed more likely, may be informative and permit some assessment of the probable diagnoses in the large group with insufficient data.

Construction of the database

At the end of each year, the results of toxin tests were reviewed and strains from patients studied because of a food poisoning incident were excluded. Toxin results plus patient details were matched to the phage typing records and the referral letters. Data from the questionnaire was then added to the database maintained over the period studied in dBII (Ashton Tate) running on Apricot computers.

The results for each case were considered as a whole and classified on the criteria listed. Phage typing results were coded to phage group with RTD typing results given greater weighting than those at RTD $\times 100$, and an opinion as to the most obvious clinical presentation was recorded.

For each year tables of the number of cases classified in each TSS category were prepared and a final retabulation of the edited data was retabulated by TSS category over the 7 years as the final database.

Analysis of the data

The yearly totals (Table 1) were not analysed statistically because the data included support for two special studies of SIDS in the late 1980s. After combining the results by TSS criteria, the primary analysis was through a χ^2 approach. Each table was treated as a valid χ^2 table and the expected values calculated from the

Table 1. *Frequency of patients allocated to clinical groups*

	1985	1986	1987	1988	1989	1990	1991	Total
Confirmed TSS	7	8	9	5	5	7	8	49
Probable TSS	13	14	6	13	6	13	14	79
Possible TSS	15	16	9	19	14	13	14	100
Unconfirmed TSS	14	12	13	14	11	13	22	99
Not TSS	19	36	38	35	34	34	23	219
No data	21	44	62	68	47	73	56	371
SIDS	1	4	11	14	9	3	3	45
Total	90	134	148	168	126	156	140	962

row and column totals. The contributions to χ^2 for each cell: ((observed-expected)²/expected), were then calculated using Supercalc 3 programs (Sorcim). The resulting tables were then examined and significant contributions to χ^2 were assessed in order of magnitude.

Toxic shock syndrome analysis

Because confirmed and probable TSS cases matched previous work, this group of results was separately analysed. Additional characters including age, menstrual presentation, tampon type, geographical distribution and sex ratio were tabulated for this group. Information from the 'Possible TSS' and 'no data' groups was excluded.

Microbiological analysis

With 997 strains of *S. aureus* tested for toxin production, retabulation of the data without clinical classification seemed useful. All 997 strains were assessed for toxin production within phage groups. Finally, the presentation of the disease was used to tabulate the phage groups of the related strains.

RESULTS

Frequencies of clinical groups over the 7-year period

Table 1 lists the number of patients classified by the clinical criteria for each year from 1985–91 inclusive. The number of cases of confirmed and probable TSS varied from 11 in 1989 to 22 in 1986 and 1991 and averaged over 18 cases per year. There was little evidence of any trend in frequency except for cases classified as 'SIDS' where support for two clinical studies in 1987–9 distort the figures. What differences remain can, to an extent, be explained by media attention including the variation in the number where insufficient data was received. For further analysis all 7 years were combined.

Analysis by clinical group

Relation of clinical group with phage group (Table 2)

A total of 997 strains from 962 patients was included. Phage group I strains were significantly more frequent in confirmed and probable toxic shock syndrome groups and were significantly under represented in the 'not TSS' group. Group III strains were significantly more frequent in the 'not TSS' group. At a lower level

Table 2. *Toxic shock. Relation of clinical group with phage group*

	Confirmed	Probable	Possible	Unconfirmed	Not	No data	SIDS	Total
I	33	47	41	28	47	119	8	323
II	0	4	8	9	19	39	4	83
III	2	6	15	14	57	57	8	159
I + III	4	2	4	12	13	32	4	71
V	4	10	11	15	33	35	6	114
42E	0	2	3	1	4	16	2	28
95	1	1	2	5	9	18	4	40
81	1	3	3	2	1	2	1	13
NT	6	8	16	17	33	62	13	155
Exptl	0	0	1	1	6	3	0	11
Total	51	83	104	104	222	383	50	997

Table 3. *Relation of clinical group with toxin production*

	Con- firmed	Probable	Possible	Uncon- firmed	Not	No data	SIDS	Total
TSST-1	12	20	20	12	22	45	4	135
A + TSST-1	23	28	22	16	14	59	3	165
Other + TSST-1	8	9	15	7	14	25	1	79
A	1	1	3	6	20	13	3	47
B	4	8	15	13	30	33	5	108
C	0	2	5	9	12	24	6	58
D	1	0	3	3	6	6	0	19
A + B, C or D	1	0	1	2	15	12	3	34
C + D	1	2	0	1	6	6	2	18
B + D	0	0	1	1	0	3	0	5
No toxin	0	13	19	34	83	157	23	329
Total	51	83	104	104	222	383	50	997

of statistical significance group III strains were under represented in the confirmed and probable TSS classifications. No other valid conclusions could be drawn.

Relation of clinical group with toxin production (Table 3)

The association of production of TSST-1, usually, and most significantly of co-production of SEA and TSST-1, with confirmed and probable TSS was evident and an excess of these toxins was seen in the possible TSS group. Production of SEA + TSST-1 was significantly lower in the 'not TSS' group than expected but SEA production with or without combination with SEB, SEC or SED was more than expected for this group. Toxin production was more common than expected in confirmed, probable and possible TSS than in the 'no data' group.

Relation between clinical group and presentation (Table 4)

The contributions to χ^2 for this table were very large mainly through the gross excesses in intestinal presentations in cases classified as 'not TSS' and in lack of presentation data in the 'no data' classification. The table is also distorted by the SIDS group. Confirmed and probable toxic shock classifications were associated strongly with a menstrual presentation and this carried over into the 'possible TSS' classification but was less frequent in the 'not TSS' and 'no data' groups.

Table 4. *Toxic shock. Presentations within clinical group*

Presentation	Con- firmed	Probable	Possible	Uncon- firmed	Not	No data	SIDS	Total
Menstrual	30	40	33	12	1	24	0	140
Septicaemia	6	7	13	18	45	36	0	125
Local	3	10	22	29	43	48	0	155
Burn	0	3	5	8	27	34	0	77
Post-op	6	12	11	12	12	17	0	70
Obstetric	1	1	3	3	1	3	0	12
Pneumonia	2	4	5	5	19	6	0	41
Other	0	0	0	2	1	0	0	3
Gut	1	0	4	3	62	8	0	78
No data	0	2	4	7	8	195	45	261
Total	49	79	100	99	219	371	45	962
Deaths	11	11	13	10	46	39	45	175

A postoperative infection was an important presentation. A septicaemic or pneumonic presentation was significantly common in the 'not TSS' group and a presentation with local infection was related to the group missing more than two criteria for TSS.

Further analysis of patients and strains classified as confirmed or probable TSS

The records of patients finally classified in the confirmed and probable TSS groups were reviewed and additional tabulations were prepared. Over the 7 years under review, this group comprised 128 cases which could be classified as meeting the criteria for confirmed or probable toxic shock syndrome (TSS). Part of this data has been presented [9]. Of the 128 cases, 67 could be classified as presenting menstrually and 55 as non-menstrual TSS. No presentation information was available for 6 cases.

Age distribution

Fig. 1 displays the age distribution for TSS with a menstrual or non-menstrual presentation within this subgroup. An age of between 15 and 20 was significantly in excess in the menstrual group as compared with the non-menstrual group. Thirty-three (49%) patients in the menstrual group were aged between 15 and 20, while only 7 (13%) of the non-menstrual group were in this age group ($\chi^2 = 18.3$, $P < 0.01$).

Tampon type

Within the menstrual presentation group, a non-introducer tampon was recorded in 24 cases and an introducer variety in 16. This is significantly different from the overall market sales (Dr G. Howarth, personal communication).

Seasonal effects

The incidence of TSS by quarter was tabulated for each year. A total of 72 cases occurred in the first half of the calendar year and 56 in the second. Although more cases were reported in the first two quarters the effect was not statistically significant.

Fig. 1. Age distribution in confirmed and probable TSS.

Geographical effects

The referring hospital of the cases of TSS was allocated to the National Health Region and compared with the number of beds available. No difference between regions was detected ($\chi^2 = 16.1$, 14 D.F., $P = 0.35$).

Sex ratio

Within the diagnosis of TSS, 23 patients were male and 105 were female, giving a sex ratio of 1:4. The sex ratio of non-menstrual cases does not differ significantly from 1:1.

Missing criteria in cases classified as probable TSS

Desquamation was not recorded in 37 of the 79 cases and hepatic and renal symptoms, headache, myalgia and mucous membrane involvement were often not mentioned. All had a rash and most showed fever, gastrointestinal symptoms and hypotension. Many showed central nervous system disturbances.

Table 5. *Phage group*

Toxin	I	II	III	I+III	V	81	95	42E	Exptl	NT	Total
TSST-1	86	10	6	6	0	7	0	2	1	17	135
A+TSST-1	141	1	4	4	1	2	0	0	1	11	165
Other+TSST-1	51	0	5	7	0	2	0	0	1	13	79
A	7	0	22	11	0	0	0	0	2	5	47
B	1	8	6	4	75	1	0	0	1	12	108
C	7	0	2	3	0	0	25	0	0	21	58
D	0	0	14	3	0	0	0	1	0	1	19
A+B, C or D	3	0	24	0	0	0	0	0	2	5	34
C+D	3	0	6	1	0	0	7	0	0	1	18
B+D	0	0	3	1	0	0	0	0	0	1	5
No toxin	24	64	67	31	38	1	8	25	3	68	329
Total	323	83	159	71	114	13	40	28	11	155	997

Analysis by phage group

Relations between phage group and toxin production for all strains (Table 5)

Very large contributions to χ^2 were seen in this table. The largest deviation (317 for the single cell) was in the association of SEB production with strains of phage group V. Almost as large (220 for the single cell) was in the association of SEC production with phage type 95 and this was supported by the association of SEC+SED production with the same phage type. Strains of phage group I produced TSST-1 usually with SEA and lacked SEB or SEC production, though toxin production of some sort was characteristic.

Phage group II strains, in this study, were non-toxin producers but it must be remembered that exfoliative toxins were not sought. Interestingly, strains of phage group III produced SEA alone or in combination with other enterotoxins or SED alone but showed reduced frequencies of TSST-1 production. In strains of phage groups I+III, only SEA production showed a significant association and this was also dissociated from TSST-1 production. Strains typing primarily with phage 42E were not toxin producers and type 81 strains were similar.

Strains recorded as not typable included an excess of SEC producers and a shortfall in strains producing SEA+TSST-1.

Relation between phage group and clinical presentation for all strains (Table 6)

The contributions to χ^2 in this table were relatively low when compared with Table 5, suggesting that disease presentation and staphylococcal phage group are not highly correlated. The principal finding was an excess of menstrual presentations in disease associated with group I strains (contribution 51 for the single cell). Group V strains were associated with either a local or a pneumonic presentation (contributions 11 and 8 respectively). Strains of group III were unlikely to present menstrually but the excess in septicæmic presentation contributed only 6.8 for this cell.

Antibiotic resistance

Toxic shock is a community disease, especially menstrual TSS and susceptibility or resistance only to penicillin is to be expected. Of the 997 strains studied, 112 (11.2%) were susceptible to the antibiotics tested and 728 (73.0%) were resistant

Table 6. *Relationship of presentation and phage group*

Phage Group	Menstrual	Obstetrics	Septicaemia	Local	Burn	Post-op	Pneumonia	Not stated	Gut	Total
I	95	3	26	45	25	21	11	75	22	323
II	3	2	11	13	8	1	5	29	11	83
III	9	1	32	23	14	14	4	43	19	159
I + III	7	0	11	12	7	9	2	22	1	71
V	1	3	13	32	12	13	11	19	9	114
42E	1	0	4	4	2	0	1	13	3	28
95	0	1	8	6	4	3	1	15	2	40
81	6	1	0	2	0	0	0	3	1	13
Exptl	1	0	2	1	0	0	0	2	5	11
NT	20	1	20	20	13	10	7	55	9	155
Total	143	12	127	158	86	71	42	276	82	997

only to penicillin. The frequency of sensitive or resistant only to penicillin varied from 92.2% in confirmed TSS to 75.6% in the 'not TSS' group. Only in this group were multi-resistant strains significantly in excess of the expected value (χ^2 13.6, $P < 0.01$).

When the antibiotic susceptibilities were examined by the phage groups of the strains, the strongest findings were excesses of multiple resistance in phage group III strains and of resistance to penicillin plus tetracycline in strains of phage group II. Phage group I strains were significantly less likely than expected to show multiple resistance and susceptibility to all agents was infrequent in phage group V. At a lower level of significance, strains of phage group I + III and NT strains were more often susceptible than predicted. While a few isolates, mainly of group III, were methicillin-resistant, this resistance was very uncommon.

DISCUSSION

The results of this study can be discussed (1) in terms of the toxic shock syndrome and its boundaries, (2) in terms of the role of toxins in severe staphylococcal infections and (3) in terms of the biology of the phage groups, the main taxonomic subdivision of the human subspecies (biotype) of *S. aureus*. The first approach through TSS questions the diagnostic criteria of the syndrome. The second hopes to define new syndromes and new therapeutic approaches while the third concerns basic science.

Toxic shock syndrome

This syndrome was defined on clinical criteria, intentionally set to be restrictive for an initial investigation [1]. Later, some latitude was permitted [5] but the definition was clearly breached when burns patients without a rash were included [13]. In this study strict adherence to the CDC criteria was the first approach. The total of 128 cases over 7 years that could be diagnosed as confirmed or probable TSS is an underestimate because of the size of group 6 with insufficient data. Because of the lack of similarity with groups 1 and 2 shown by group 6, the amount of underestimation is unlikely to be much more than half, indicating around 40 cases of TSS in the UK per year. These findings are not inconsistent

with earlier reports [14]. The results of this study show that cases classified as 'possible TSS' with two criteria missing or not reported showed similar characters to those classified as confirmed or probable TSS when clinical presentations (Table 4) and TSST-1 production (Table 3) were considered, although there was little microbiological support. The presentation as local infection linked even cases with more than two criteria missing into the wider syndrome. What is then the boundary of TSS or should more than one disease be recognized? Overall, a disease which can be called 'menstrual toxic shock' seems to exist. Most affected are teenage girls who perhaps do not follow hygienic advice well, who are inexperienced tampon users and use a non-introducer tampon. Group I strains producing TSST-1 alone, or with other enterotoxins, usually SEA, are implicated. The course of the disease is swift and may be fatal within hours of the first alarm. Therapy must be prevention by education in personal hygiene backed up by provision of immunological reagents against tumour-necrosis factor and other immunologically active substances in casualty at least.

A very similar disease appears to result from infection with a group V strain producing SEB but rarely presents menstrually (Table 6) [6, 10]. There is some suggestion that lethality is a character of SEB intoxication but this was not confirmed in this study. It is uncertain whether the selection criteria for this study would exclude comparable cases without a recorded rash. Surely, there are clinical symptoms that can separate TSST-1 disease from SEB disease within TSS that can be defined. The association of SEB with burns patients has been suggested since the early Scandinavian studies [18].

Other toxic disease

When the role of these toxins in disease states other than toxic shock syndrome is questioned, the results of this study allow some conclusions.

Strains of phage group III were significantly associated with a 'not TSS' classification of the case (Table 2), with production of SEA in the absence of TSST-1 but with or without co-production of other enterotoxins (Table 3) or of SED (Table 5) and tended to lead to a septicaemic presentation (Table 6). The increased antibiotic resistances of this type of strain supports the idea of a septicaemic syndrome quite separate from the two TSS diseases.

The association of phage group V, the main producers of SEB (Table 5) with local sepsis or a pneumonic presentation (Table 6) would suggest that the excess of local infections in the clinical group missing more than two TSS criteria (Table 4) might reflect lesser degrees of a syndrome related to TSS. However, the deviations from expected values in Tables 2 and 3 were not significant.

Phage group as a predictor of toxin production

The results presented in Table 5 strongly relate toxin production and the phage group of the strain irrespective of clinical classification. Strains of phage group I produce TSST-1 and often other enterotoxins but rarely are non-toxigenic. Phage group III strains do not usually produce TSST-1 but SEA and SED are favoured. Mixed I+III strains produce SEA; group V, SEB and 95 strains SEC quite predictably. This supports the idea that phage grouping embodies biologically similar strains.

Other groupings

Isolates from patients classified as possible TSS, unconfirmed TSS, SIDS and, to a large extent, the 'no data' group, showed little deviation from the expected values (Tables 2 and 3) and displayed significant negativity in the other tables. This could be interpreted as cases where the staphylococcus investigated was not relevant to the patient's condition through misdiagnosis, chance or multiple infection. The mainly negative findings in the large 'no data' group restrain estimates of the true frequency of TSS.

CONCLUSIONS

Toxic shock syndrome affected about 20–40 patients each year with no apparent secular trends. An excess of TSS cases occurred in females aged 20 or less using a non-introducer tampon.

Menstrual TSS is associated with phage group I strains producing TSST-1, often with SEA.

Group V strains may produce SEB and were associated with local infections and pneumonia.

Group III strains produce SEA and other enterotoxins but not TSST-1. They are associated with septicaemia but not with TSS.

Strains typing only with phage 95 are likely to produce SEC and be associated with a menstrual presentation of toxic disease.

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