Toxic Shock Syndrome

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Staphylococcal scarlet fever, recognised in 1927, is characterised by toxaemia, a generalised erythematous rash and subsequent desquamation. In 1978 Todd *et al.*[1] described a 'new' disease in children in which fever, myalgia, erythema and desquamation were associated with *Staph. aureus* infection. They coined the term Toxic Shock Syndrome (TSS). Subsequently this pattern of disease was described in healthy young women in the USA. Extensive controlled epidemiological investigations later identified the association of TSS with menstruation, tampon usage and the presence of *Staph. aureus* in the genital tract.

Epidemiology

Since 1979 more than 2,500 cases of TSS have been reported in the USA. Of these, 96 per cent have been females, of whom 95 per cent have been associated with menstruation and tampon use[2]. The number of cases reported since 1980 has declined and this is attributable to a decrease in retrospectively reported cases and possibly to changes in the pattern of tampon manufacture and usage, following the publicity associated with this syndrome. It is interesting to observe that eight states contributed more than 60 per cent of cases reported in the USA[3]. This may also reflect differences in population immunity, prevalence of toxin-producing staphylococci or, more likely, the intensity of interest and surveillance.

The prevalence of TSS in the USA far exceeds that in any other country, including Canada. Cases have been recognised in Western Europe and Australasia, but have not yet been reported in developing countries. Up to April 1984, only 88 confirmed or probable cases meeting the definition of the Center for Disease Control (CDC) had been identified in the UK. All but 15 were associated with menstruation. This incidence in the UK is much lower than that in the USA and may reflect a true lower frequency, reduced tampon usage or failure to recognise the syndrome.

Non-menstrual cases account for about 13 per cent of those reported in the USA[2,4]. The mean age for menstrual TSS is 22.6 years, 65 per cent of diagnoses being made in women under 25 years, although only 45 per cent of tampon users are in this age group. Non-menstrual TSS patients tend to be slightly older, reflecting the greater age distribution of post-partum and post-surgical cases. Racial differences have been recognised in the USA, 96 per cent of menstrual cases occurring in whites, who represent 83 per cent of tampon users[5].

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Clinical Features

TSS is a multi-system disease with a wide range of symptoms and signs. There is at present no specific laboratory test and diagnosis is based on clinical features. The criteria of the widely accepted definition, formulated by the CDC in 1979[6] and subsequently modified to include orthostatic syncope and patients with staphylococcal bacteraemia[3], are summarised in Table 1.

Menstrual TSS

Prodromal symptoms may occur and include malaise, myalgia, low grade fever, vomiting, diarrhoea and vaginal discharge. However, in many instances the onset is abrupt, with fever, rigors, myalgia, pharyngitis, conjunctivitis, severe hypotension, vomiting, diarrhoea and generalised skin rash[7,8]. Headache and abdominal tenderness may also occur.

The findings on the skin and mucous membranes are among the most characteristic of the disease. The rash occurs early and is usually diffuse, erythematous and blanches on pressure. There may be quite marked oedema of the face, limbs and perineum. A petechial rash may also develop in response to thrombocytopenia or disseminated intravascular coagulation. About 5-10 days into the illness, a discreet maculo-papular rash may develop and be mistaken for a drug eruption. Mucosal abnormalities are common, with conjunctivitis, pharyngitis, 'strawberry tongue' and vaginal hyperaemia. There may be multiple punctate ulcers of the cervix and vagina.

Desquamation occurs in half the patients 1-2 weeks after onset of the illness but may be delayed for up to 21 days. It predominantly affects the palms and soles, especially around the nails, but may be generalised. Delayed loss of nails and hair may also complicate severe disease.

Vomiting and effortless watery diarrhoea occur in

Table 1. Case definition, toxic shock syndrome. (Revised by the Center for Disease Control, 1982.)

Fever	≥38.9°C (102°F)	
Rash	Diffuse macular erythroderma	
Desquamation	1—2 weeks after onset of illness	
Hypotension	Systolic BP ≤90 mmHg or orthostatic hypotension	
	≥15 mmHg or orthostatic dizziness	
Multi-system involvement	Three or more of the following:	
	Gastrointestinal:	vomiting or diarrhoea
	Muscular:	severe myalgia or ↑ CPK × 2 normal
	Mucous membrane:	vaginal, oropharyngeal or conjunctival hyperaemia
	Renal:	urea or creatinine ↑ × 2 normal or >5 WBC/HPF in urine
	Hepatic:	total bilirubin, AST, ALT ↑ × 2 normal
	Haematological:	platelets < 100 × 10^9/litre
	CNS:	disorientation or altered consciousness without focal neurology
Other conditions should be excluded		

almost 90 per cent of patients at onset. There is generalised abdominal tenderness, frequently accompanied by guarding and reduced bowel sounds, but without rebound tenderness. Although often severe, these symptoms generally subside within 72 hours. Diffuse myalgia and muscle weakness are common and many patients complain of exquisite skin and muscle tenderness when touched or moved. Arthralgia, sterile joint effusions and low grade synovitis are uncommon.

Hypotension and profound shock are cardinal features of TSS and may be associated with electrocardiographic abnormalities such as conduction defects and ischaemic changes. Acute oliguric renal failure may complicate the presence of profound hypovolaemic shock. Pulmonary oedema is common and may be associated with haemoptysis or the adult respiratory distress syndrome; headache, confusion, irritability, aggression, hallucinations and photophobia may be prominent.

The CDC definition was restrictive to provide epidemiological homogeneity in case-controlled studies. Many patients do not show the full features of this definition. Such cases are in general milder, and often without significant fever, erythema and shock[9,10].

Non-Menstrual TSS

TSS has complicated a variety of medical and surgical conditions in non-menstrual females, males and children, but is rare under the age of 10 years[2]. The non-menstrual variant shows the same clinical features as the menstrual form and is broadly divided into three categories of staphylococcal infection: (i) associated with abortion or childbirth in which it may complicate both Caesarean and vaginal delivery; (ii) associated with cutaneous or subcutaneous infections including surgical wounds, abscesses, cellulitis, fasciitis, burns and secondarily infected herpes zoster, and (iii) a smaller heterogeneous group complicating deep-seated infection such as osteomyelitis, endocarditis, pneumonia and empyema[5].

Laboratory Findings

A broad range of laboratory abnormalities is recognised and reflects widespread tissue ischaemia of various organs rather than the direct effect of a toxin. Frequently reported abnormalities include neutrophilia, profound lymphopenia, normochromic normocytic anaemia and thrombocytopenia. Changes in coagulation include prolonged prothrombin and partial thromboplastin time and may presage disseminated intravascular coagulation[7].

Renal involvement is reflected in oliguria, raised serum urea and creatinine, trace proteinuria and sterile pyuria[11]. Elevated liver enzymes and bilirubin are common although frank jaundice is rare. Electrolyte abnormalities may include hyponatraemia, hypokalaemia, hypophosphataemia and hypocalcaemia which in part may be secondary to raised calcitonin levels[12]. Elevated creatinine phosphokinase concentrations are proportional to skeletal muscle involvement.

Cervical and vaginal cultures will yield *Staph. aureus* in most menstrual cases [10], while in non-menstrual cases a focus of sepsis should be sought. Although no specific diagnostic test for TSS exists, the demonstration of toxin production by isolates together with a characteristic history or progression to desquamation is strong evidence for the diagnosis. The absence of detectable antibody to toxin in the convalescent phase is also consistent with the syndrome[13].

Differential Diagnosis

The differential diagnoses vary both with the predominant organ system involved and geographically. The variety of differential diagnoses in the UK is listed in Table 2.

Treatment

The immediate management is directed towards the restoration of circulating blood volume and the maintenance of adequate tissue perfusion. Electrolyte solutions, colloids or whole blood are appropriate. Large volumes may be required in combination with vasopressor agents. Hypoxaemia should be reversed and may require mechanical ventilation. The requirements for haemodynamic monitoring, mechanical ventilation, as well as the arrest of bleeding by infusing platelets and fresh frozen plasma can more easily be managed in an intensive care setting.

Table 2. Differential diagnosis of toxic shock syndrome.

Exanthematous conditions
Drug eruptions
Erythema multiforme
Streptococcal scarlet fever
Leptospirosis
Meningococcaemia
Toxic epidermal necrolysis
Staphylococcal scalded skin syndrome
Kawasaki disease
Gastrointestinal conditions
Infectious gastroenteritis
Staphylococcal food poisoning
Miscellaneous conditions
Septic shock
Systemic lupus erythematosus
Pelvic inflammatory disease
Haemolytic-uraemic syndrome
Acute pyelonephritis

Tampons should be removed in menstrual cases. The value of antiseptic vaginal douches has not been assessed in a controlled manner. In non-menstrual cases, the focus of infection should be sought and the need for surgical debridement or drainage assessed. Antibiotics are indicated to eliminate the source of toxin production and to prevent recurrent disease; their use probably does not reduce the duration of the acute illness[9]. As most staphylococci implicated in TSS produce β-lactamases[14], flucloxacillin is an appropriate choice. Duration of treatment has not been established in controlled trials, although a course of less than 10 days does not consistently eradicate colonising staphylococci.

The place of corticosteroid therapy is not established, although anecdotal reports suggest that early administration reduces both height and duration of fever, together with the degree and distribution of erythroderma and subsequent desquamation[15].

Once life-threatening complications are controlled, improvement is usually rapid, with dissolution of fever within 72 hours, and the rash and myalgia over the course of 5-10 days. Laboratory abnormalities similarly return to normal. Prolonged sequelae are rare, although muscle weakness, myalgia, impaired memory and concentration may persist[16].

Mortality ranges from 2-13 per cent, but has shown a progressive fall each year since the description of the syndrome[2]. This may be attributed to a greater number of fatal cases reported retrospectively in the early years, or to the more rapid recognition and treatment of the condition as physicians have become aware of the syndrome. Death may result from refractory cardiac arrhythmias, adult respiratory distress syndrome, pulmonary haemorrhage and disseminated intravascular coagulation.

Recurrent Disease

TSS has also been characterised by a tendency to recur. The peak recurrence rate of 65 per cent has fallen[7] with earlier recognition and more aggressive treatment with antibiotics. Most recurrences have occurred within two menstrual periods after the initial attack and are generally less severe[9]. Recurrence in non-menstrual TSS is rare because the focus of infection is more readily recognised. Antibody to the toxin is often absent or in low titre in those with recurrent TSS and may represent a specific immune defect.

Pathogenesis and Pathology

The pathogenesis of TSS is not entirely understood but reflects the interaction between *Staph. aureus,* a specific toxin and a non-immune patient. Staphylococcal colonisation of the vagina has been demonstrated in over 85 per cent of menstrual TSS cases[10]. In controlled and uncontrolled studies, vaginal colonisation by *Staph. aureus* among healthy women varies between 0-17 per cent and peaks immediately after the onset of menstruation and post-partum[17]. However, increased adherence of staphylococci to vaginal epithelial cells has not been demonstrated in either normal persons or TSS patients [18].

Colonisation appears to be higher in women with contraceptive diaphragms or intrauterine devices, which suggests that fingers may be a source of these organisms[17]. In both the USA and UK, strains of *Staph. aureus* associated with TSS are predominantly β-lactamase producing and belong to phage group I, especially types 29 and 52[19]. Such strains appear to be more resistant to inactivation by heavy metals such as arsenic, cadmium and mercury[20]. Lysogenic induction of toxin production has not been demonstrated[21].

Staphylococci are biologically extremely active and produce a variety of toxins and virulence factors including enzymes. The strains originally isolated by Todd *et al.*[1] showed variable production of an epidermal toxin which was subsequently shown to have no aetiological association with TSS[22]. Later two other candidate toxins were described. Bergdoll *et al.*[23] isolated staphylococcal enterotoxin F (SEF) from 91 per cent of 142 strains of *Staph. aureus* associated with menstrual TSS. Later this 22,500 dalton protein was renamed toxic shock toxin (TST). On further purification it was called toxic shock marker protein (TSMP), as its emetic action in monkeys was not consistently reproducible. Schleivert *et al.*[24] described another toxin—pyrogenic exotoxin C (PEC)—identified in all 119 strains of *Staph. aureus* associated with TSS, since it produced a pyrogenic response in rabbits. Further immunochemical characterisation has confirmed that the biologically active moiety of both SEF and PEC is identical and this has now been named toxic shock syndrome toxin-1 (TSST-1)[25].

More than 60 per cent of people over 10 years of age and 88 per cent of individuals over 20 years have antibodies to TSST-1[26]. Bergdoll *et al.*[13] postulated an apparently isolated immunodeficiency in TSS patients, as only 15 per cent develop antibodies to TSST-1 in the convalescent phase. This finding has been confirmed in British patients.

The association between toxin production and the development of pathogenicity is not well understood.

Staph. aureus isolated during the 1950s have been shown to produce TSST-1 and the prevalence of antibodies in a general population in 1960 appears similar to that in 1980[27]. Furthermore, 10-50 per cent of *Staph. aureus* isolated from the genitalia of healthy females produce TSST-1 which by extrapolation suggests that between 1-5 per cent of females are at risk of developing TSS. However, attack rates in the USA have varied between 5-17/100,000 women[28], considerably lower than the predicted figure, and therefore other factors must be involved in the development of the disease. Tampons, particularly of the high absorbency variety, have been implicated in several case control studies[29]. Tampons have been shown to stimulate toxin production to varying degrees although they do not enhance staphylococcal growth[30]. It has been suggested that tampons absorb substrates from the vagina, which normally inhibit staphylococcal growth[31]. Alternatively, aerobic Gram-negative bacteria may enzymatically degrade the carboxy-methylcellulose in tampons, resulting in an environment rich in carbohydrates and conducive to staphylococcal growth[32]. Most recently it has been shown that TSST-1 is a potent inducer of interleukin-1 (endogenous pyrogen) and this may explain many of the features of TSS[33]. However, it must be remembered that to date TSST-1 has not been identified in the blood or urine of affected patients.

In general, the pathological findings reflect tissue ischaemia secondary to poor perfusion[34]. There is minimal evidence of an inflammatory reaction and no evidence of bacterial tissue invasion. Acute tubular necrosis, pulmonary oedema and haemorrhage and acute fatty infiltration of the liver are all commonly found. A round cell infiltrate, together with congestion and oedema of the myocardium, correlates with clinical evidence of cardiac involvement.

The only characteristic lesions seen are microscopic mucosal ulcerations in the cervix and vagina, with tissue separation occurring below the basal layer. These changes have also been described in the oesophagus and bladder and have been attributed to an action of the toxin and not to tampon damage. Skin biopsies have shown desquamation below the basal layer in association with a perivasculitis, but no evidence of immune complex deposition.

Prevention

A number of suggestions for reducing the risks of TSS in susceptible patients has been made. Most are a logical extension of our current knowledge of the epidemiology and pathogenesis of this condition but few have been proven in controlled studies. Avoidance of tampon use would eliminate the risk of menstruation-associated disease but is impractical. Intermittent use might be a compromise although more realistically high absorbency tampons might be avoided, unless absolutely necessary. No information is available on the advantages of more frequent changing of tampons.

Vaginal colonisation by staphylococci might be decreased by the use of applicators rather than fingers for insertion of tampons. While the frequency of recurrence is demonstrably reduced by appropriate antibiotic treatment, the potential for re-colonisation with *Staph. aureus* remains. Thus patients who have recovered from menstrual TSS should ideally be advised to discontinue tampon use, since monitoring of vaginal and cervical cultures for toxin-producing staphylococci is both insensitive and impractical. However, it should be remembered that the risk of recurrence is greatest within three months of an initial attack. Education of both tampon users and medical staff to recognise early symptoms and signs remains the cornerstone of management.

The Future

Our understanding of TSS has advanced greatly in a very short time. Nevertheless, some fundamental questions remain. As yet, no specific diagnostic test is available and research in this direction is urgent. Although not a common condition in the UK, the varied nature of the clinical manifestations of the syndrome means that TSS may present to a broad range of clinicians—general practitioners, surgeons, obstetricians and gynaecologists, intensive care specialists and psychiatrists as well as general physicians. The advice of the CDC to physicians remains true in that a diagnosis of TSS should be considered 'in all patients with appropriate symptoms and signs, regardless of the patients' age, sex, race and menstrual status'.

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The Great Plague of 1665

Far from the City of London the Rev. Ralph Josselin sat in his vicarage at Earls Colne, Essex, and wrote up his diary for 28th May 1665 '. . . my personal illness abateth, blessed bee God. The plague gott into our land at Yarmouth and London, 14 dying this weeke.' He was a bit late with the news for the plague had come from The Netherlands via Yarmouth to London in November 1664. Indeed in March 1665 there was no Presidential election at the College, its business being disrupted by the plague, and Sir Edward Alston continued as President. Things could not have been too bad as on April 15th the King made his first visit to the College, listened to the Lumleian lecturer, George Ent, and knighted him on the spot. But on May 17th, at the request of the Privy Council, Comitia discussed measures to be taken against the plague. This was not too difficult as the measures recommended were virtually the same as those published by the College in 1625, 1630 and 1636.

Plague had stalked the land for many years and there were many statutory and administrative measures to operate whenever an epidemic threatened. The Plague Relief Act of 1604 had empowered local authorities to raise a tax for the relief of distress and to appoint watchers to ensure that those infected or likely to be infected should be kept in their houses. Anyone found abroad with an infectious sore was liable to the death penalty as a felon. Very oddly the powers of this Act were not to be exercised in the universities of Cambridge and Oxford (the Act has them in that order), within the precincts of any cathedral church in England or within the colleges of Eton and Winchester.

Apart from the watchers, each epidemic saw the appointment of searchers and bearers, all swearing an oath of office. The searcher was bound to 'diligently viewe and search the Corps of all such persons as dureing theis infectious times shall dye . . .' He also had to follow definite rules. 'Yee shall decline, and absent yourselves from your familys, and allwaies avoide the societye of people and in your walke shall keepe as far distant from Men as may be allways carrying in your hands a white wand by which the people may know you and shunn and avoide you.' The bearer swore that he would 'beare to the ground and bury the bodies of all such persons as . . . shall die of the pestilence . . . carrying them to buriall alwaies in the nightyme.' He also had to carry a white wand.

All this organisation could do nothing against the rapidly increasing epidemic in the City of London. On 12th June 1665, the College, at the request of the Lord Mayor, nominated eight physicians for a plague service in the City. Of these, two were chosen, Nathaniel Hodges and Thomas Witherley, and two volunteered 'upon principles of honour and conscience', Nicholas Davys and Edward Deantry. It appears that at least 24 physicians remained in the City of whom 17 were Fellows of the College or elected later. Five surgeons and seven apothecaries are also known to have stayed to work. By that autumn five physicians (including Pepys' doctor, Alexander Burnett), and three surgeons were dead. The College lost its apothecary, William Johnson, but the four Fellows named above survived.

The long hot dry summer turned the City into a charnel house; only the watchers and searchers were on the streets, with the dead carts rumbling through the night. After the June Comitia the College did not reassemble for nine months. An astrologer showed how the

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epidemic was due to the planets and added that the plague only attacked 'persons of narrow souls and understandings'; 'those of a more refined reason' escaped. Indeed reason, abetted by money, made many flee the City. A good many physicians left urgently for the country where they joined their rich patients. On July 9th Rev. Josselin wrote 'The plague feares the London. They flie before it and the country feares all trade with London . . . The Lord stay his heavy hand.'

The Lord did not stay his heavy hand. During August and September there was a period of 30 days when over a thousand died each day in the City. Many churchmen thought the plague was a punishment from God, as shown in a book titled *God's Terrible Voice;* while 'Theological Queries' contained advice on the ethics of fleeing the plague or visiting the sick, it also advised the taking of tobacco in the morning against the infection. Of more medical importance was the quick reprinting of Dr Francis Herring's book on the plague which he had published in 1628, his advice then being the same as that given officially by the College.

By early winter the worst was over in London. The plague still ravaged Essex towns. Josselin recorded this, adding in wonderment 'yett Colne, sinful Colne, is spared'. But it was not until 1st February 1666 that the King returned to Whitehall. He made some modest awards for service during the great plague when he met his Privy Councillors on May 16th. The College was not mentioned and only two physicians, Drs Astell and Inard, neither Fellows of the College, received a piece of inscribed plate to the value of £10. The Council was still uncertain as to the cessation of the plague, as it continued to prohibit public burials 'during the time of infection'. Plague of course did return to London that summer of 1666 but was never severe. More was seen in the country. In July Josselin wrote 'A very hot season. Plague rageth at Braintree, Colchester. At London abated . . .'

Of course the whole City of London was to change in terms of density of population and plague. On Sunday, 2nd September 1666, the first flames of the Great Fire started to purge the City of infection. The coming of winter as usual brought the plague to a halt in other towns. Wrote Josselin: 'Nov. 25. A very wett morning. The country clear of the plague.'