A cluster of cases of streptococcal necrotizing fasciitis in Gloucestershire

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SUMMARY

We describe the first cluster of cases of necrotizing fasciitis (NF) in this century in the United Kingdom (UK). Between 1 January and 30 June 1994 there were six cases (five confirmed, one probable) of *Streptococcus pyogenes* NF in west Gloucestershire, population 320000. Two cases died. The first two patients probably acquired their infections during the course of elective surgery performed in the same operating theatre, possibly from a nasopharyngeal carrier amongst the theatre staff. The remaining infections were community-acquired. Of 5 *S. pyogenes* isolates there were 2 M1 strains, 1 M3, 1 M5 and 1 M non-typeable strain. *S. pyogenes* NF had not been recorded in west Gloucestershire in the preceding 10 years and the incidence of *S. pyogenes* bacteraemia in England and Wales had not risen in the past 5 years.

The two presumably theatre-acquired infections raised several issues. The need for detailed bacteriological investigation of all cases of post-surgical NF was confirmed. Clusters of *S. pyogenes* infection following surgery should be managed by closure of the operating theatre until all staff have been screened for carriage. Closure of an operating theatre and screening of staff following a sporadic case is probably not justified because of the infrequency of surgical cross-infection with *S. pyogenes*. Regular, routine screening of theatre staff is neither practical nor necessary.

INTRODUCTION

Necrotizing fasciitis, a term first coined by Wilson in 1952 [1], is a rare disease whose incidence in the UK is not known precisely. A similar condition was described by Hippocrates as a complication of erysipelas [2]. Outbreaks of 'malignant ulcer', 'hospital gangrene' and 'phagedena', all probably the same condition, occurred in Nelson's navy and in hospitals and military barracks in the 19th century [3]. Necrotizing fasciitis appears to be very closely related to

Fournier's gangrene [4], Meleney's hemolytic streptococcus gangrene [5] and synergistic necrotizing cellulitis [6–8]. The frequency with which *S. pyogenes* is the primary cause of, or contributes to NF may vary with time. Meleney [5] and others [9, 10] reported haemolytic streptococci as the major bacterial pathogen, but with improving standards of anaerobic microbiology the polymicrobial nature of most of these infections has become apparent [11, 12]. In Giuliano's study, 13 of 16 patients were infected with mixed aerobic and anaerobic faecal bacteria, whereas only three patients yielded *S. pyogenes*, in each case without anaerobes [11].

The speed of progression of *S. pyogenes* NF is greater than could be explained by direct bacterial multiplication and local spread. Progression may therefore involve bacterial dissemination via lymphatics and/or diffusion of bacterial cytotoxins through lymphatics or along tissue planes, with tissue death occurring ahead of bacterial colonization. Local tissue necrosis is frequently accompanied by severe systemic manifestations of toxæmia, including hypotension, impaired renal function and disordered blood coagulation [13]. The systemic symptoms are similar to those of the streptococcal toxic shock-like syndrome [14].

The mortality of NF is high in most series (25% or more), including those of recent years [12, 13, 15–18]. Age, diabetes, intravenous drug abuse, hypertension, malnutrition and obesity have been associated with higher mortality [12]. It is unclear whether NF caused by *S. pyogenes* alone carries a higher risk of death than the polymicrobial form of the illness. Immediate, wide surgical excision of affected tissues is the mainstay of treatment, with high doses of intravenous antibiotic. Circulatory, respiratory and renal support may also be required, together with control of disordered blood coagulation.

Trends in the epidemiology of serious *S. pyogenes* infections have varied markedly between countries recently. Neither *S. pyogenes* bacteraemia nor *S. pyogenes* NF are notifiable conditions in the UK, but the numbers of cases of *S. pyogenes* bacteraemia in England and Wales reported to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) have remained essentially unchanged over the last few years, with approximately 500 episodes reported annually. The incidence of scarlet fever, which is notifiable, has not risen recently. There has been no rise in the number of cases of *S. pyogenes* NF in France within the last 4 years [19]. This contrasts with recent experience in Scandinavia and in the USA where changes in *S. pyogenes* serotypes have been accompanied by a rise in the numbers of serious *S. pyogenes* infections including NF [20–22, E. A. Høiby, personal communication].

S. pyogenes strains are classified on the basis of antigenic variations in the cell surface M protein. The M protein confers resistance to phagocytosis and is an important virulence factor [23]. The prevalence of particular M types of *S. pyogenes* is known to fluctuate widely within communities over periods of 10 or more years [24], and some M types such as M1 and M3 are particularly associated with invasive disease and fatal infections [21, 24]. *S. pyogenes* strains producing streptococcal pyrogenic exotoxin A (SPE A) are also known to be associated with serious and invasive infections [25]. The *speA* gene can be carried on a temperate bacteriophage [26] and it has been proposed that the upsurge in serious streptococcal infections observed in the latter half of the 1980s in the USA could

Table 1. *West Gloucestershire patients with S. pyogenes necrotizing fasciitis, 1994*

Patient	Age	Sex	Address	Date of onset or admission	Predisposing factors	Microbiology/ Histology	Outcome*
A	66	M	Stroud	05.02.94	Elective hernia repair	Positive serology; Gram-positive cocci seen in tissues	S
B	64	F	Stroud	07.02.94	Elective varicose vein operation	<i>S. pyogenes</i> M1	S
C	64	M	Stroud	17.02.94	—	<i>S. pyogenes</i> M3	S
D	52	M	Gloucester	07.04.94	Diabetic cardiomyopathy	<i>S. pyogenes</i> non-typeable	D
E	62	F	Forest of Dean	13.04.94	Obesity, diabetes, history of deep vein thromboses of right leg	<i>S. pyogenes</i> M5	D
F	46	F	Stroud	11.05.94	—	<i>S. pyogenes</i> M1	S

* S, survived; D, died.

Patient A is classified as a probable case using the PHLS Action Group case definition [29]. The remaining patients are classified as confirmed cases.

be due to specific clones of different M types whose virulence has been enhanced by infection and lysogenization by temperate phages carrying this gene [27].

Epidemiology of the Gloucestershire cluster of cases

Demographic and clinical details of the six cases, including outcome, are summarized in Table 1. Four of the six were aged 60 or more. The two patients who died both had pre-existing medical conditions, and one (patient D) was already in very poor health.

Patient A

Patient A underwent a routine operation of bilateral mesh inguinal herniorrhaphy on 4 February 1994, at a community hospital serving the Stroud area of west Gloucestershire. He became pyrexial the next day and 36 h after the operation was found collapsed, with signs of shock. He was transferred to the local district general hospital where a diagnosis of Fournier's gangrene was made. Intravenous antibiotics were commenced together with immediate wide excision of affected skin and subcutaneous tissues. Tissue was sent for histological but not bacteriological examination.

Patient B

Three days later (7 February), patient B underwent a routine sapheno-femoral disconnection for varicose veins in the same operating theatre. The following morning the patient began vomiting and had diarrhoea; gastroenteritis was suspected. The patient became hypotensive and was transferred to the district general hospital in the early hours of 9 February. NF was suspected, broad-spectrum intravenous antibiotics were commenced and surgery arranged. The

diagnosis was confirmed at operation. The affected tissues were excised and specimens sent for culture and histology. Chains of Gram-positive cocci were seen in tissue sections and later, *S. pyogenes* was isolated.

Actions and investigations following the second case

The community hospital operating theatre was closed. The remaining patients on the same operating lists as patients A and B, together with the patients from the intervening list were contacted. The integrity of the theatre ventilation system and autoclaving procedures were checked. The operating theatre was re-cleaned and subjected to environmental sampling. Nose and throat swabs were obtained from all operating theatre staff who had been involved in either list, from ward nursing and medical staff involved in pre- and post-operative care of the affected patients, and from the patients themselves. Anal and vaginal swabs were not obtained. The histology sections from patient A were reviewed. Additional epidemiological links between the two patients were sought.

Results of investigations following the second case

The two patients resided in the same village in the Stroud area but had had no prior social contact. The 13 other patients who had undergone operations between 4 and 7 February were well. No faults were found in the theatre ventilation system nor in autoclaving procedures; *S. pyogenes* was not isolated from any of the swabs taken in the operating theatre. Nose and throat swabs from the two affected patients did not yield *S. pyogenes*, though by then, both had received broad-spectrum antibiotics.

Sections of excised tissue from patient A showed chains of Gram-positive cocci, compatible with streptococci. No other bacteria were seen. A week later, a serum sample from this patient showed an anti-streptolysin O titre of 400×10^3 units/ml and an anti-DNAse B titre of > 5760 units/ml. *S. pyogenes* was detected in two members of the operating theatre staff. One was heavily colonized in both nose and throat; the other was a scanty throat carrier only. The heavily colonized member of the theatre staff assisted in operations on both the affected theatre lists and also during operations on the intervening list. During the first affected list she was anaesthetic nurse and during the second acted as a general assistant. In line with current local practice for these duties, during neither list did the member of staff wear a mask, nor scrub up.

The PHLS Streptococcus Reference Laboratory found the *S. pyogenes* strains from patient B and from the heavily colonized staff carrier to be type M1; the second staff carrier was colonized with an M6 strain. The M1 carrier member of staff may therefore have been the source of infection. This member of staff had experienced an upper respiratory infection with sore throat about 3 weeks earlier, but in accordance with local policy had consulted a general practitioner (GP), received and taken a course of antibiotics and had been off work until fully recovered. Nose and throat swabs were not obtained during the original illness nor prior to the member of staff returning to work.

Carriage was eliminated from both members of staff with a course of amoxycillin (augmented by nasal mupirocin ointment in the nasal carrier) before they

returned to work. The marital partner of the M1 carrier member of staff was colonized with the same strain, and was also treated successfully by the same method. The operating theatre was reopened on 15 February.

Patient C

On 18 February NF was diagnosed in a patient admitted to the district general hospital from the community. This patient lived within 1 km of patients A and B. There was no recent connection between patient C and the community hospital and there were no apparent predisposing factors. Infection spread from the area of the right achilles tendon. At operation, necrosis of deep, as well as superficial tissues was found, and the patient underwent below and then above knee amputations of the right leg. *S. pyogenes* in pure culture was isolated from the excised tissue.

Actions and investigations following the third case

While awaiting the results of streptococcal typing, the possibility of a community-wide outbreak of *S. pyogenes* NF was considered. GPs and hospital doctors throughout the county and neighbouring consultants in communicable disease control were alerted. GPs in the Stroud area were asked to swab patients with sore throats or with skin lesions.

The *S. pyogenes* strain from patient C was type M3 and the same strain was isolated from seven family members with whom he had been in recent close contact. The appeal to GPs yielded approximately 50 *S. pyogenes* strains which were of heterogeneous M types.

Patient D

A fourth patient, previously in poor general health, was admitted to the district general hospital from Gloucester city (15 km from Stroud) on 7 April. He was a diabetic with advanced cardiomyopathy. He presented with septic arthritis and *S. pyogenes* was isolated from a knee aspirate and from blood cultures. Subsequently an area of necrosis developed in his oedematous scrotum, necessitating excision of tissue. Histology confirmed NF and Gram-positive cocci in chains were seen in tissue sections. The infection was controlled but the patient died of heart failure a few days later. The *S. pyogenes* strain was M non-typeable.

Patient E

On 13 April a fifth patient with NF was admitted to the district general hospital from the Forest of Dean (40 km from Stroud). She was an obese diabetic with a past history of deep vein thromboses of the right leg. She developed blistering on the right leg which spread to the flank and inguinal area on the day of admission. A large area of skin and subcutaneous tissue was excised from the upper thigh and lower abdomen. Despite surgery and antibiotics, the patient died. *S. pyogenes* type M5 was isolated from the excised tissue.

Patient F

A sixth patient from the Stroud area was admitted to the district general hospital on 11 May. She gave a 10-day history of sore throat and 2 days before

admission had developed a fever and joint pains. On admission she had a severe toxic shock-like syndrome. She developed a purpuric rash on the limbs with blistering. A piece of necrotic muscle and skin was excised from her thigh. *S. pyogenes* M1 was isolated from blood cultures.

Media reaction

A frenzy of worldwide media interest ensued [28] which lasted about 3 weeks. The press officer at PHLS HQ recorded more than 1000 enquiries and the Gloucester Public Health Laboratory and Department of Public Health Medicine responded to more than 200 requests for information. Many health districts and laboratories throughout the UK received enquiries.

Actions and investigations following the cluster of six cases of S. pyogenes necrotizing fasciitis

Following the reporting of the sixth case a PHLS Action Group met at PHLS HQ, Colindale, London; the Action Group agreed a number of measures. A case definition for *S. pyogenes* NF was established and published, accompanied by recommendations for antibiotic treatment of suspected cases [29]. The Gloucestershire cluster was reviewed against the case definition. Patient A was classified as probable; the remainder of the cases were confirmed. No additional control measures were recommended, but further investigation of the bacterial isolates was agreed.

Examination of the epidemiology of *S. pyogenes* infections in England and Wales showed no evidence of any recent increase. A search for unreported cases of *S. pyogenes* NF in the first 6 months of 1994 was commissioned. Twenty-five cases (18 fatal) were identified in England and Wales [30]. A system for enhanced surveillance of serious *S. pyogenes* infections was established.

Histological sections from patient A were subjected to polymerase chain reaction using *S. pyogenes*, *speA*, *speB* and *speC* DNA sequences as primers. Amplicons of a size consistent with the presence of both *speA* and *speB* were obtained. No amplicons were obtained from negative control tissue samples, but the M1 *S. pyogenes* strains from patient B and from the colonized staff member with whom patient A was epidemiologically linked, also yielded amplicons consistent with the presence of *speA* and *speB*.

Other cases of necrotizing fasciitis in west Gloucestershire from 1 January to 30 June 1994

There were four cases of non-streptococcal NF ascertained during the first 6 months of 1994. All were community-acquired infections. None of the affected patients was so seriously ill as the *S. pyogenes* NF cases.

Serious S. pyogenes infections in west Gloucestershire from 1 January to 31 December 1994

In the latter half of 1994 there were no further cases of *S. pyogenes* NF identified in west Gloucestershire, but throughout the year there were five further cases of serious *S. pyogenes* infection; two were post-operative, of whom one patient died.

Table 2. *Invasive group A streptococcal infections ascertained in west Gloucestershire (positive blood cultures and cases of confirmed NF), 1994*

Week no.	Date	Patient	Clinical diagnosis	Bacteriological diagnosis	GAS type*
5	04.02.94	A†	NF	Raised ASO titre; positive histology and PCR	—
6	07.02.94	B†	NF	Tissue isolate	M1
7	18.02.94	C†	NF	Tissue isolate	M3
14	04.04.94	GQ	Cellulitis	Blood culture	nd
14	07.04.94	D†	NF; died	Knee aspirate and blood culture	nt
15	13.04.94	E†	NF; died	Tissue isolate	M5
19	11.05.94	F†	NF	Blood culture	M1
27	06.07.94	AD	Cellulitis	Blood culture	M22
27	09.07.94	MJ	CAPD peritonitis	CAPD fluid	M5
36	09.09.94	JW	Cellulitis	Blood culture	M-T28
37	13.09.94	JK	Hysterectomy; died	Blood culture	M-T3

* nt, non-typeable; nd, not tested.

† These patients are the same six cases of necrotizing fasciitis described in Table 1.

The remaining three infections were community-acquired. The details are given in Table 2.

DISCUSSION

An outbreak can be defined as 'two or more cases of an illness associated in time and place [31] or an unexpected increase in the incidence of a disease. Six cases of *S. pyogenes* NF occurred in west Gloucestershire during the first 6 months of 1994, an infection not identified in this population in the preceding 10 years. However, at least four different serotypes of *S. pyogenes* were implicated. Two infections occurred following elective surgery; the remainder were community-acquired. Five of the six cases were confirmed by culture and met the PHLS Action Group case definition [29]. The sixth case, patient A, had clear-cut clinical NF, the same epidemiological exposure as patient B (a confirmed case), and high streptococcal antibody titres. Tissue samples showed Gram-positive cocci in chains on direct microscopy and yielded gene sequences strongly suggestive of *S. pyogenes* infection. This patient was classified as a probable case [29].

The unusual feature of the cluster is not that the affected patients suffered from serious *S. pyogenes* disease but that infection manifested itself as NF in all cases. Outbreaks of NF have not been reported in the UK during this century. In the USA it has been estimated that NF comprises 5–10% of all invasive *S. pyogenes* infections [32], whereas in west Gloucestershire only four other cases of invasive *S. pyogenes* infection (one bacteraemic) were identified in the first 6 months of 1994.

The first two patients were probably infected during elective surgery. Surgical cross-infection due to *S. pyogenes* is well recognized but uncommon [33–35]. Clusters of cases of post-surgical *S. pyogenes* NF have not been reported before. Perhaps surprisingly, in most published accounts of hospital outbreaks, anal or

vaginal carriers have been the source of infection [36–44]. Anal and vaginal swabs were not collected from theatre staff in this investigation.

Could patient A's infection have been prevented? A naso-pharyngeal carrier amongst the theatre staff was the most likely source of the two post-surgical infections. The dose of bacteria initiating infection in each case may have been small, as only 2 of the 15 patients who were exposed to the carrier during operations performed between the 4 and 7 February 1994 became infected. The M1 carrier member of staff did not scrub for any of the three pertinent operating lists and wore a mask during only one of the lists. Nasal carriage of *S. pyogenes* is less frequent than throat carriage but nasal carriers are more likely to disseminate bacteria [45]. Individuals are also more likely to disseminate *S. pyogenes* during and immediately after upper respiratory infections [46].

Following the two theatre-associated cases, we tested the feasibility of recommending that operating theatre staff with respiratory infections, especially if accompanied by sore throat, should be screened for nasal and pharyngeal carriage of *S. pyogenes* before returning to work, but found this policy to be unworkable.

Could the second case of post-surgical infection have been prevented? Bacteriological investigation of tissue specimens from patient A was not undertaken. Even had a *S. pyogenes* strain been isolated from patient A's tissue specimens, it would not have been consistent with current UK practice to close the operating theatre or to investigate the entire operating theatre team after a single case of *S. pyogenes* wound infection.

S. pyogenes infection developing early in the post-operative period is likely to have been acquired intra-operatively, either endogenously or from a member of the theatre team. For sporadic cases, the proportions of endogenous and exogenous infection are not known. Early post-operative cases of NF should be investigated carefully to identify those due to *S. pyogenes*. In view of the rarity of outbreaks, investigation of theatre staff, which logically should include anal and vaginal, as well as nose and throat swabbing, would be highly intrusive, and is not justified. A single negative set of screening swabs may not be sufficient to declare a treated carrier free of colonization, and successfully treated carriers could be reinfected by their colonized partners.

The theatre environment is an unlikely source of contamination and closure of operating theatres after sporadic cases of *S. pyogenes* infection cannot be recommended. Theatre closure has serious implications for resources and for surgical waiting lists, as well as inconveniencing patients. However, the occurrence of two or more cases of early post-operative *S. pyogenes* infection within a short time period does warrant immediate closure of the operating theatre and full investigation of all staff as detailed above.

In the latter half of 1994 an operating theatre at our district general hospital was closed for investigation following a further sporadic case of serious (and ultimately fatal) post-operative *S. pyogenes* infection. The investigation took 4 days and led to the loss of four operating sessions. No streptococcal carriers were identified among the theatre staff, and the infection was presumed to have been endogenous.

Can a rational explanation be found for this cluster of infections in west

Gloucestershire, which was due to *S. pyogenes* of different M types? Four explanations, not necessarily exclusive, have been advanced. Reporting bias is possible but unlikely, because of the extreme severity of *S. pyogenes* NF [13].

The cluster could have occurred by chance. Though serious *S. pyogenes* infections had been recorded sporadically in west Gloucestershire before 1994, *S. pyogenes* NF had not been observed in the preceding 10 years. The likelihood of six cases of *S. pyogenes* NF occurring by chance in a population of 320 000 in a 6-month period is very low [30]. Nevertheless, in the absence of any other explanation, this must remain a possibility.

Alternatively, the population of west Gloucestershire could have been rendered transiently susceptible to serious bacterial infections by some external agent, for example a wave of virus infection in the community [47]. There was no evidence to support this hypothesis. Numbers of cases of other bacterial infections were apparently unchanged during the same period. Further, such an explanation would not account for an excess of cases of *S. pyogenes* NF unaccompanied by an increase in other types of invasive streptococcal disease.

Finally, a gene or genes conferring enhanced virulence and an enhanced capacity to cause tissue necrosis could have infected multiple different M types of *S. pyogenes* circulating within this community. However, if this was the case, it is not clear why the 'outbreak' should have come to an end.

In a recent study, streptococcal protease activity was significantly associated with NF [48]. The *speA* gene which is associated with streptococcal virulence can be found in streptococcal temperate phages [26] and Vesela and colleagues have shown that invasive isolates of M1 *S. pyogenes* (M1 Inv) carry a bacteriophage conferring enhanced invasion of human epithelial cells, *speA* production, and a unique DNA restriction profile [49].

Though several different serotypes of *S. pyogenes* were implicated in the Gloucestershire cluster, evidence for horizontal genetic interchange between different clones of *S. pyogenes*, probably mediated by bacteriophage, is now beginning to accumulate [25]. Haase and colleagues have shown that *S. pyogenes* strains of different M types may share the same electrophoretic (ET) type, i.e. they may be clonally related [50]. The possibility that genes conferring increased virulence may be transmitted between different *S. pyogenes* M types by bacteriophage would be consistent with the current upsurge in invasive streptococcal disease observed in Scandinavia and the USA. A comparative study of *S. pyogenes* strains from cases of NF (including the Gloucestershire strains), from cases of invasive streptococcal infections in which NF was not a feature, and from asymptomatic carriers, is now underway and will be reported elsewhere. For the present, careful genetic analysis of representative *S. pyogenes* isolates from the UK will now be required.

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