

A double outbreak of exfoliative toxin-producing strains of *Staphylococcus aureus* in a maternity unit

J. DAVE¹, S. REITH², J. Q. NASH³, R. R. MARPLES² AND C. DULAKE³

¹*Leeds Public Health Laboratory, Bridle Path, York Road, Leeds LS15 7TR*

²*Staphylococcus Reference Laboratory, Hospital and Respiratory Infection
Division, PHLS Central Public Health Laboratory, 61 Colindale Avenue,
London NW9 5HT*

³*Ashford Public Health Laboratory, The William Harvey Hospital,
Kennington Road, Willesborough, Ashford, Kent TN24 0LZ*

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SUMMARY

This report describes a double outbreak of staphylococcal scalded skin syndrome (SSSS) in which two distinct tetracycline-resistant strains of *Staphylococcus aureus* producing different exfoliative toxins were involved. In the first phase the daytime staff of the delivery unit and eczematous skin conditions in midwives were implicated as the probable source. In the second phase a source within a post-natal ward was suggested with local cross-infection. In the final phase both sources were epidemiologically linked to cases of SSSS. Because early discharge was the policy of the unit many cases presented in the community rather than in the hospital.

Confirmation of epidemiological findings was provided by additional laboratory studies. Two distinct strains of *S. aureus* could be defined, differing in phage-typing patterns, the exfoliative toxin produced, plasmid profile, cadmium resistance and bacteriocin production. Strict care in hand washing with a chlorhexidine-containing detergent was an important control measure.

INTRODUCTION

Staphylococcal scalded skin syndrome (SSSS) was separated as a distinct entity from toxic epidermal necrolysis (TEN) as originally described [1] when an extracellular exfoliative toxin was detected by Melish and Glasgow [2]. They extended the syndrome to include not only extreme forms in which the blistering rash is generalized leaving a raw area resembling a burn and requiring similar management but also milder localized disease such as pemphigus neonatorum and impetigo. The separation of SSSS from TEN was confirmed by clear histological distinctions: in SSSS the split occurred in the stratum granulosum of the epidermis while in drug-induced or idiopathic TEN the split was between the basal layer and the dermis [3]. In the early work a strong relationship between SSSS and phage group II strains of *Staphylococcus aureus* producing exfoliative toxin was demonstrated [2] but toxin production by strains of other phage groups was soon detected [4]. A second exfoliative toxin was described [4, 5] and unlike the first

Requests for reprints: J. Dave.

toxin ETA, this toxin, ETB, was plasmid mediated. Other uncharacterized toxins may exist with similar effects. The susceptibility of the newborn mouse or adult hairless mouse to these toxins [2, 4] may be the only method of detection of a new toxin.

The syndrome, SSSS, is most often diagnosed in neonates and children but may occur in the immunocompromised patient [6] and rarely in healthy adults [7] while non-staphylococcal TEN is usually a disease of adults, often drug related [3]. Immunological status seems important. In an outbreak in a newborn nursery where maternal antibody may still be present, mild cases are most frequent and severe, life-threatening disease, seen in older children, is unusual. As the blisters form within the epidermis in SSSS, in the absence of super infection, healing does not involve scarring but the morbidity in the baby is real and the concern of the mother equally needs a satisfactory medical response [8].

Nursery outbreaks of SSSS are usually caused by a single toxin producing strain of *S. aureus* and can be large [9, 10]. The strain is usually of phage group II but an outbreak caused by a strain of phage group I + III producing ETA has been described [11].

Here we describe a complex nursery outbreak in which two strains could finally be distinguished by their epidemiology, toxin type and in other strain characters.

METHODS

Epidemiological methods

Recognition of a potential outbreak

Microbiology request forms describing two babies with skin lesions suggestive of SSSS were received by the local laboratory early in July. Both had been recently delivered in the same maternity unit. Midwives were alerted and screening of babies and staff was instituted.

Case definition

Provisionally, a potential outbreak case was defined as a neonate with a blistering or peeling skin occurring within 21 days of delivery or as the isolation from a neonate of a tetracycline-resistant *S. aureus*. Ultimately a confirmed case was defined as a neonate from whom a tetracycline-resistant, exfoliatin-producing *S. aureus* of phage group II was isolated. Most displayed signs of SSSS.

The birth register as a source of information for epidemiology

The birth register provided information about time of delivery, names of staff members present during labour and details of any complications. Examination of the register provided a rapidly available short list of midwives who were present during the delivery of affected babies. Crude attack rates could be calculated for any implicated midwives. Information obtained helped strengthen the case for removing from duty three midwives, two of whom were suffering from eczema.

Other sources of information for epidemiology

Following the onset of the outbreak, detailed information concerning the neonates, mothers and staff was obtained from several sources; laboratory reports, midwives' duty rosters and mothers' and neonates' notes. All mothers

were contacted by telephone and asked to answer a standard questionnaire which included questions on the site and type of lesions, the presence of symptoms, whether antibiotics were administered and if the babies had recurrence of symptoms.

Laboratory methods

Local laboratory methods

Isolation of Staphylococcus aureus. Prior to the identification of the outbreak, swabs submitted from affected neonates by the obstetric unit and by general practitioners were routinely cultured using conventional methods by direct plating on blood agar. Following recognition of the outbreak all swabs from neonates were also subcultured onto blood agar after enrichment in 7% salt broth. The outbreak strains were tetracycline resistant and this was used as an immediate marker.

Screening of neonates on the day of discharge from the ward. Swabs from nose, axillae, groin and umbilicus obtained from neonates were placed together in a salt broth medium and incubated for 18 h at 37 °C before plating out. Swabs from neonates with skin lesions were cultured separately.

Screening of staff. Staff were screened with swabs obtained from nose, throat, axillae and any visible skin lesions. Finger-print cultures using blood agar plates were obtained from eczema sufferers. Swabs received were cultured using salt enrichment broths.

Reference laboratory methods

Phage typing. The isolates were typed at routine test dilution (RTD) and at RTD × 100 with the international phages by standard methods [12, 13].

Antibiotic screen. Susceptibility was tested on Isosensitest agar (Oxoid CM471) to penicillin (1 IU), tetracycline (10 µg), erythromycin (10 µg), fusidic acid (10 µg), kanamycin (30 µg), gentamicin (10 µg) and methicillin (10 µg) disks in standard disk diffusion methods [14].

Exfoliative toxin production. Strains were grown in a modified sac culture system [15]. Briefly double-strength broth was dispensed in 5 ml volumes in dialysis tubing. A sealed tube was placed in a Universal bottle and 2.5 ml of PBS outside the dialysis tubing was inoculated with the test strain. After incubation for 24 h on a roller, a sample of 200 µl was removed from the outer compartment for testing for the presence of ETA and the system reincubated for a further 24 h before testing the outer compartment for the presence of ETB. In this system, the organism grown in 7.5 ml of nutrient space but large extracellular molecules such as the exfoliative toxins are confined to 2.5 ml.

The presence of each toxin was detected by agarose double-diffusion against standard antisera (a gift from Dr J. de Azavedo). Identity of precipitin lines with known ETA and ETB producers and with part-purified toxins was required.

Plasmid analysis. The lysostaphin-Brij 58 method of Degener and colleagues [16] as modified for *S. aureus* [13] by miniaturizing for microfuge was employed. DNA was precipitated with an equal volume of cold isopropanol and held overnight at -20 °C. After centrifugation and alcohol removal the pellet was resuspended in 25 µl of distilled water and 10 µl of loading buffer (glycerol 6.6 ml, distilled water 13.4 ml, bromophenol blue 10 mg) was added before loading the gel

Table 1. *Clinical details obtained on neonates*

Neo-nate	Site	Lesion	Antibiotics Y/N	Toxin	Relapse Y/N
1	Whole body	Spots	Yes		Yes
2	Neck/ear/armpits/ groin	Blister	Yes	No specimen	No
3	Groin/leg	Blister 29 mm	Yes	B	Yes
4	Neck/arms/legs	Blister 29 mm	Yes	No specimen	No
5	Neck/groin/axilla	Blister 29 mm	Yes	B	No
6	Face/abdomen	Blister 2 mm	Yes	No specimen	No
7	Hand/neck/finger/ underarm	Blister	Yes	B	Yes
8	Upper body	Red eye, blister 5 mm	Yes	B	Yes
9	Upper body	Blister	Yes	No specimen	No
10	Face/elbow/groin/ shoulder	Sticky eye, blister 20 mm	Yes	B	Yes
11	Umbilicus/groin	No lesions	Yes	B	No
12	Face/neck	Blister 27 mm	Yes	B	No
13	Axilla/neck/groin	Blister 29 mm	Yes	B	No
14	Underarm	Blister 20 mm	Yes	---	No
15	Abdo/groin/legs	Blister 2 mm	Yes	B	No
16	—	No lesions	No	B	No
17	Lower body	Sticky eye, no lesions	Yes	---	No
18	—	No lesions	No	B	No
19	Axilla neck	Sticky eye, tiny heat spots, no blisters	Sterzac powder	---	No
20	Head	Blister	Yes	---	No
21	—	No lesions	No	A	No
22	Head/chin	Blister 10 mm	Yes	A	Yes
23	Neck/shoulders	Blister	Yes	A	No
24	—	No lesions	No	A	No
25	—	Sticky eye, no lesions	No	---	No
26	Abdo/groin/finger	Blister 29 mm	Yes	A	Yes
27	Face/arm/leg	Blister 11 mm	Yes	A	Yes
28	Groin	Blister 0.5 mm	Yes	A	No
29	—	No lesions	No	A	No
30	—	No lesions	No	A	No
31	—	No lesions	No	A	No
32	Bottom leg	Blister 0.5 mm	No	B	No
33	—	No lesions	No	B	No
34	Elbow/bottom	Blisters 22 mm	Yes	A	No
35	All over the body	Macular rash, no blisters	Yes	B	No
36	Groin	No blisters, (white heads)	Yes	B	No
37	Arms/neck	Sticky eye, blister 25 mm	Yes	B	Yes
38	Face	Blister 10 mm	No	A	No
39	Arm/neck/groin	Sticky eye 15 mm, blisters	Sterzac powder	B	No
40	Nose/eyelids	Blister 20 mm	Yes	B	No
41	—	Tiny white heads, no blisters	Sterzac powder	---	No
42	—	No lesions	No	---	No

(0.7% agarose in TRIS-borate buffer). Electrophoresis at 100 V for 3–4 h was carried out, the gels stained with ethidium bromide (1 mg/l) and the bands visualized under transmission u.v. and photographed. Two strains of *Escherichia coli* V517 [17] and 39R 861 [18] were included as size controls. Plasmid curing was attempted by incubation at 42 °C for 5 days and by ethidium bromide, subculturing from the first clear tube of a dilution series.

Heavy metal and other resistances. Incorporation plates were prepared containing cadmium sulphate 10 mg/l, mercuric chloride 5 and 10 mg/l, ethidium bromide 50 mg and propamidine 100 mg/l. Selected isolates were applied with a rod inoculator and growth after 24 h at 37 °C was recorded. Standard MIC studies of tetracycline were performed.

Bacteriocin production. Lawns of *Corynebacterium renale* NCTC 11140 [19] and *S. aureus* NCTC 10804 (502A [10]) were prepared on nutrient agar. Wells were cut out with a cork borer and filled with supernate from a centrifuged overnight broth culture of the test isolate. The plates were incubated for 18 h at 37 °C. Any zone of inhibition was considered positive.

RESULTS

The outbreak

The obstetric unit consisted of a labour ward and three postnatal wards extending down a common corridor. The labour ward staff were separate from the postnatal ward staff. The outbreak occurred in three distinct phases. The first seemed to be related epidemiologically to daytime births on the labour ward, the second to a local problem in a single postnatal ward and in the third both epidemiologies coexisted though the labour ward was prominent (Table 1).

Phase I

The outbreak was detected on 9 July when two neonates who had been recently discharged from the maternity unit developed SSSS. Discharge swab isolates had already been sent to the reference laboratory. Over the following 24 h inquiries carried out by midwives revealed that, in a further eight neonates, SSSS had occurred before 9 July. The neonates had varying stages of a blistering skin rash and had been delivered during the previous 10 days.

The affected neonates had all been delivered between 09.00 and 18.30 h (63 unaffected babies out of the 116 neonates born in June were born outside these hours; $\chi^2 = 10.8$, $P < 0.01$). The affected neonates were spread across the 3 postnatal wards and were under the care of 2 of the 4 consultant obstetricians.

Detailed examination of the birth register revealed that one of the midwifery sisters had been present at 4 out of the 5 cases delivered between 30 June and 2 July (later identified as carrier B). Examination of the duty rosters indicated that no single staff member could be linked to all the cases.

The discovery of a further seven affected babies in the community all delivered during daytime confirmed the link with daytime staff. Enquiries on the ward revealed that two midwives suffering from eczema of their hands had been present at the delivery of 12 of the 17 affected neonates. Both admitted to using soap rather than chlorhexidine for hand cleansing because of the discomfort caused by

disinfectant on their skin. The number of infected babies delivered by carrier B rose to 8 out of 9 babies between 3 and 8 July (the ninth baby was a still birth). The second midwife with eczema (carrier A) had been present at the delivery of four of the affected neonates. Two further cases of SSSS occurred after 9 July giving a total of 19 affected neonates.

Pending laboratory results these two midwives were removed from duty on 10 July. Subsequently tetracycline-resistant *S. aureus* resembling isolates from the affected babies were isolated from carriage sites of both carrier A and carrier B and from a third midwife who had been applying lotion to the back of carrier A. After these staff changes no further isolates of tetracycline-resistant *S. aureus* were made for 2-3 weeks.

Phase II

The second phase of the outbreak began on 2 August and was identified as a result of the continued routine screening of neonates on discharge for carriage of tetracycline-resistant *S. aureus*. Unlike phase 1 of the outbreak, affected neonates were equally divided between day and nighttime deliveries over an 11-day period. However, of the 16 neonates on one ward, 12 were colonized. During this time period, 24 unaffected neonates were nursed on the other three wards ($\chi^2 = 25.7$, $P < 0.01$). A tetracycline-resistant *S. aureus* was also isolated from a baby bath used on the same ward. No carriers were found amongst ward staff.

Phase III

A third cluster of cases occurred following the return of carrier A to duty on the labour ward on 8 August. A cluster of 11 neonates with SSSS were identified using the provisional case definition. Six out of 14 neonates delivered by carrier A during this period developed skin lesions. Her eczema was noted to have relapsed shortly after her return to duty.

Carrier A was removed from duty on 16 August and swabs confirmed recrudescence of the tetracycline-resistant *S. aureus*. Routine screening of discharged neonates was continued for a further 6 months until the outbreak had clearly finished.

Laboratory results

Over the course of the outbreak, 495 babies were born. Over the full 11-week period 42 neonates met the provisional case definition, 19 in phase one, 12 in phase two and 11 in phase three, and extended the outbreak back in time to early June (Fig. 1). Strains were available for phage typing and toxin testing from 38 babies. Of these, 22 were symptomatic, the strain typed as group II and was toxigenic, 7 producing ETA and 15, ETB; 8 were asymptomatic carriers of a toxigenic strain, 5 producing ETA and 3, ETB. In 5 symptomatic babies the strain tested was non-toxigenic, 3 typing weakly in group II and 2 typing 42E, and 3 asymptomatic babies yielded strains not of group II. Ultimately, a case was confirmed as a neonate from whom an exfoliative toxin-producing, tetracycline-resistant *S. aureus* of phage group II was demonstrated. Thirty babies met these more rigorous criteria; all 11 in phase I yielded *S. aureus* which produced ETB, 10 in phase II carried ETA-producing strains and in phase III 7 produced ETB and 2 ETA. Blisters covering various sites on the body were detected on 21 of the 42

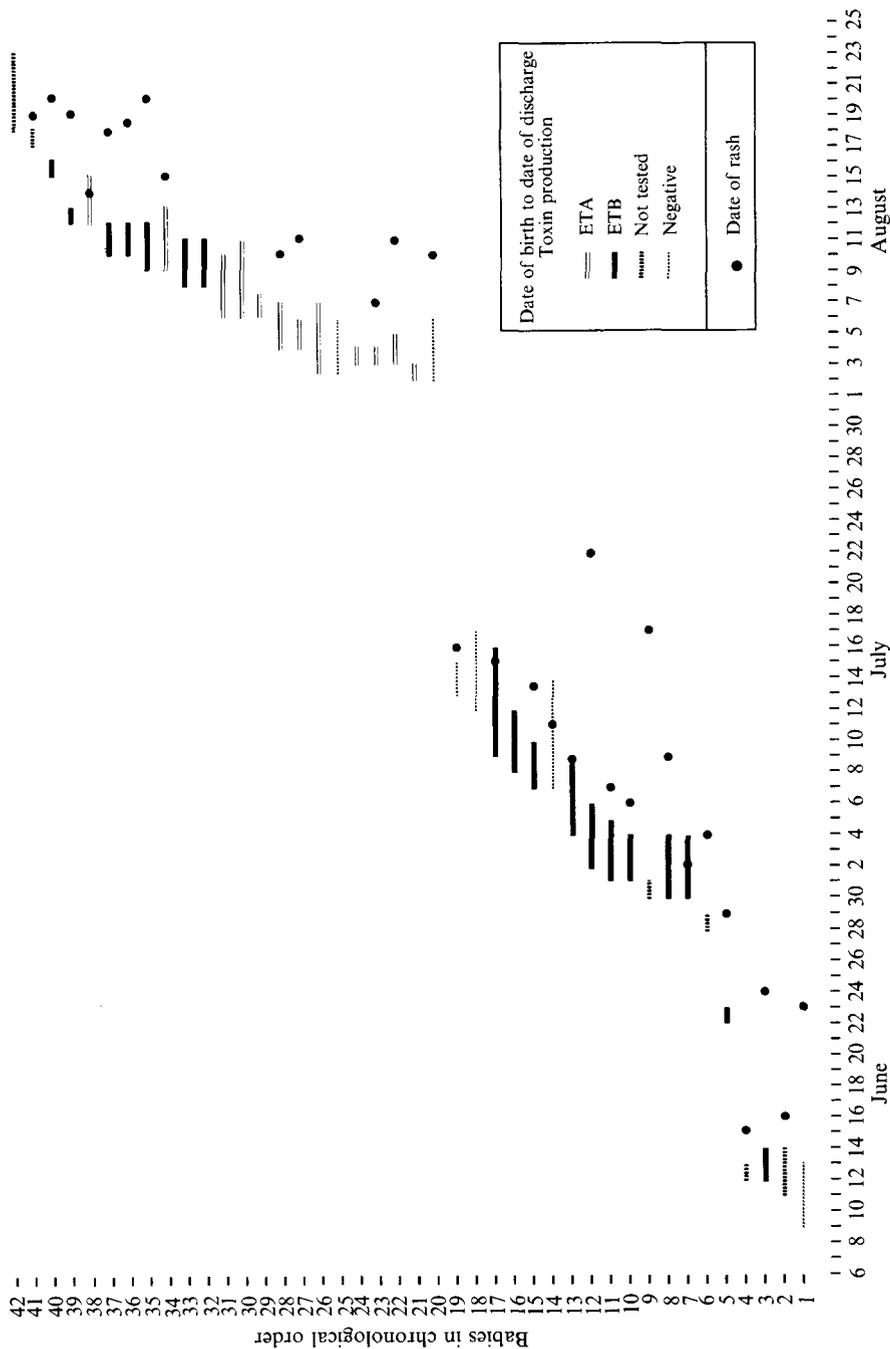


Fig. 1. Progression of the outbreak. The bars indicate days in the unit; dots the appearance of the rash. Note the frequency of development of symptoms after discharge.

neonates. These varied in size from 2 to 29 mm. Some of the neonates also had sticky eyes, macular rash or tiny whiteheads. Although there were more ETB producers associated with blisters (12 of 18) than ETA producers (7 of 12), the association was not statistically significant. Antibiotics were administered to 27 neonates with an additional 3 neonates receiving Sterzac powder (Hough, Hoseason & Co.). Despite antibiotics relapse occurred in nine neonates.

Early reference laboratory results

The first isolates from this outbreak were received in the reference laboratory on 9 July when the outbreak was recognized. Both initial strains typed strongly at RTD with 3A, 3C, 55, 71 and were tetracycline-resistant. Further isolates were received and the existence of an outbreak was confirmed by 18 July. Exfoliative toxin results, available by 2 August, associated the isolates with the strong group II pattern with the production of the much less frequent exfoliative toxin, ETB. This further supported the occurrence of an outbreak. No further studies seemed indicated at that time.

Later reference laboratory results

Isolates of tetracycline-resistant *S. aureus* continued to be sent for typing and isolates typing very weakly at RTD and reacting weakly with 3 of the 4 group II phages at RTD $\times 100$ suggested that either a new strain was present, some phenotypic change in the outbreak strain had occurred, or that the typing phages had changed. The last was unlikely because of satisfactory quality control results. The relationship of the weak group II isolates with production of ETA made the hypothesis of a new strain the most tenable. Later, when the differences in epidemiology were recognised, both strains could be confidently identified within the isolates submitted.

The division of the isolates into two strains based on phage typing and toxin production was tested in 130 isolates received from 79 babies, 14 mothers, 9 nursing, medical and laboratory staff and from the environment.

Thirty-six isolates were allocated to strain 1 and 20 isolates to strain 2. Seventy-four isolates could be excluded, 11 as non-typable and the rest with other phage patterns. The characteristics of the two outbreak strains are listed in Table 2.

The two strains differed in exfoliative toxin produced, in plasmid profile, cadmium resistance and in *C. renale* bacteriocin production. Neither strain was resistant to mercury, ethidium bromide or propamidine. Neither produced a bacteriocin active against *S. aureus* NCTC 10804.

Curing of the 3.1 Kb plasmid in both strains was associated with the loss of resistance to tetracycline. ETB mediators were not defined.

Control measures

Following identification of the outbreak the Infection Control Team instituted the following control measures:

(1) All medical and nursing staff on the obstetric wards were screened for carriage of *S. aureus* (later restricted to tetracycline-resistant strains). Follow up of the paediatric staff was restricted to those identified in the case notes or birth register as having attended affected babies.

Table 2. Characteristics of the two outbreak strains

	Strain 1	Strain 2
Group II phage strength	Strong	Weak
Exfoliative toxin	ETB	ETA
Plasmids	42.3 Kb, 9.1 Kb, 3.1 Kb.	33.2 Kb, 3.1 Kb.
MIC of tetracycline	40 mg/l	40 mg/l
Cadmium resistance	—	+
<i>C. renale</i> bacteriocin	+	—
Isolates	36 (4 staff)	20 (0 staff)
Present in Phase 1 ...	+	—
Phase 2 ...	—	+
Phase 3 ...	+	+

(2) All babies were screened before discharge from hospital for carriage of *S. aureus*. Neonates found to be positive for tetracycline-resistant *S. aureus* were examined for signs of SSSS.

(3) Staff were reminded of the appropriate infection control measures including the importance of hand washing with chlorhexidine before and after contact with different neonates.

(4) Existing guidance on the use of gloves in the labour wards was reinforced.

(5) Two midwives with eczematous lesions on their hands and the third carrier were immediately removed from duty.

(6) All community midwives were asked to report neonates with suspicious skin lesions by telephone to the Infection Control Team who followed them up.

(7) Neonates with SSSS were treated with a 5-day course of flucloxacillin.

Clinical course of affected neonates

Most of the neonates made an uneventful recovery but nine neonates had relapse of symptoms (Table 1).

Eradication of carriage of Staphylococcus aureus

Members of staff identified as carriers of tetracycline-resistant *S. aureus* were removed from duty and treated with a 5-day course of rifampicin 600 mg, nasal mupirocin and chlorhexidine shampoo applied daily in a shower or bath. They were allowed to return to work when three negative post-treatment screens were obtained using appropriate enrichment cultures.

DISCUSSION

Investigation of outbreaks of the staphylococcal scalded skin syndrome (SSSS) in the newborn nursery often, but not always [9, 20], involves not only primary phage typing and antibiotic susceptibility patterns but also additional studies to delimit the outbreak. Such studies often disclose other incidents of transmission separate from the main outbreak but not a second outbreak as described above. Dancer and coworkers have reported a biphasic single outbreak [8] and by reverse typing and plasmid profiles could separate this outbreak from the larger one in the following year although both strains typed 3A/3C [10]. In the first outbreak, a separate toxigenic strain typing weakly with 55 was recovered from an affected baby and a staff carrier. Heat treatment, *in vivo* toxin assays and plasmid profiles

were needed by Dowsett and colleagues [19] to show that five babies yielding a toxigenic non-typable strain related to group III formed an outbreak. At the same time another strain typing 3A/3C/55/71 was recovered from an affected baby, a sibling and a staff member and several mother–baby pairs were detected. Other characters were concordant.

In the present study two distinct strains caused epidemiologically different outbreaks in the same summer. Extra laboratory studies involving the reference laboratory were needed to confirm and support the findings of the local hospital-based infection control team. Although one strain was epidemiologically related to the labour ward and the second caused a local ward incident, there was no clinical difference in the disease symptoms. Dancer and coworkers noticed differences [10]: in their first outbreak the babies displayed generalized SSSS while in the second, localized pemphigus neonatorum was the clinical presentation.

Exfoliative toxin B production without coproduction of ETA is unusual but the rates apparently vary between countries. This toxin has been associated with plasmid mediation and thus can occur in other than group II strains. Kondo and colleagues [5] reported 15% of group II isolates in Japan to produce ETB, and de Azavedo and Arbuthnott found 14.3% for group II strains but only one of 32 (3.1%) for non-group-II UK strains as producers of ETB alone [21]. Piemont and colleagues [22] report a study of 2632 *S. aureus* isolates where of 163 ET producers, only six isolates (4%) produced ETB alone. In that series 131 toxigenic isolates types with the group II phages. Here the finding of ETB production in 26 isolates from 18 infants and 10 isolates from 4 staff carriers was sufficient evidence to support the epidemiological conclusion of a major outbreak.

An important aspect of this investigation was the recognition that early discharge from a maternity unit meant that cases would present in the community. In previous descriptions, the detection of discharged cases has depended on the local laboratory also serving the community [11, 19] or, as here, by active search. In this study more than half the babies affected in the first phase of the outbreak had left hospital before diagnosis. Eight toxin-producing strains were recovered from the nine patients in relapse. Five produced ETB and three produced ETA.

Staphylococcal lesions other than blisters suggest the presence of other circulating strains of staphylococci. The relatively high relapse rate after apparently adequate antibiotic therapy has not been described previously, though relapse after treatment has been noted [10].

In phase II the phage-typing results, while not conclusive, supported a different epidemiology from phase I but the determination of ETA production by these somewhat different strains confirmed the local interpretation. In phase III when both strains were circulating, exfoliative toxin production became the definitive criterion.

It was felt necessary to confirm the identification of each isolate. The classical markers that have been used to characterize group II strains have been plasmid profiles, resistance to heavy metals and antibacterials and production of a bacteriocin active on *Corynebacterium renale* [8, 10, 19]. The results clearly distinguished the two strains (Table 2). The tentative suggestion that strain 1 producing ETB was more virulent than strain 2 was supported by a local laboratory infection of an MLSO who developed a blistering rash on the fingers

from which strain 1 was recovered. The localization of the lesions suggests that some degree of systemic immunity leads to local lesions [23].

The importance of eczematous skin lesions as a source of infection from members of staff was very clear in phases 1 and 3 of this outbreak. In some previous reports [11], eczema has been significant and the high frequency of transmission recorded here would imply that eczematous skin conditions should be a reason for exclusion of staff from the delivery unit and probably from the postnatal wards. Perhaps this needs official guidelines.

Prophylaxis with antibacterial agents in the newborn is controversial. Gezon and co-workers [24] advocated hexachlorophane (HCP) and for many years this was the accepted regimen. Concern about toxicity grew [25] and hexachlorophane became difficult to use prophylactically. Topical chlorhexidine as an alternative to hexachlorophane has not been investigated fully. Marples and colleagues [26] recommend a single bath with 4% chlorhexidine as appropriate. The best regime for healthy babies is yet to be defined though quite complex protocols have been suggested [10]. In this study chlorhexidine appeared to help in the control of the outbreak but the lack of compliance by the midwives with eczematous skin lesions indicates that surveillance of control measures may be necessary. The question of how far prophylaxis should be pressed in the absence of clearly transmissible infection is raised by outbreaks such as we describe. Mupirocin may be needed to control carriage [9].

These studies demonstrate the role of local laboratory, reference laboratory, local epidemiology and occupational health departments in the control of an outbreak. Here communication with the wards, laboratory and reference facilities led to early recognition of an outbreak and rapid development of screening tests. Reference laboratory findings confirmed the occurrence of a second strain but communication with the occupational health service could have been better. It is clear that the guidelines that now operate are insufficient to prevent SSSS.

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