Identification and control of a gentamicin resistant, meticillin susceptible *Staphylococcus aureus* outbreak on a neonatal unit

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Abstract

We describe the identification and control of an outbreak of gentamicin resistant, meticillin susceptible *Staphylococcus aureus* (GR-MSSA) on a 36-bed neonatal unit (NNU) in London. Control measures included admission and weekly screening for GR-MSSA, cohorting affected babies, environmental and staff screening, hydrogen peroxide vapour (HPV) for terminal disinfection of cohort rooms, and reinforcement of hand hygiene. Seventeen babies were affected by the outbreak strain over ten months; seven were infected and ten were asymptomatic carriers. The outbreak strain was gentamicin resistant and all isolates were indistinguishable by pulsed-field gel electrophoresis. The outbreak strains spread rapidly and were associated with a high rate of bacteraemia (35% of 17 affected patients had bacteraemia vs. 10% of 284 patients with MSSA prior to the outbreak, $p=0.007$). None of 113 staff members tested were colonised with GR-MSSA. GR-MSSA was recovered from 11.5% of 87 environmental surfaces in cohort rooms, 7.1% of 28 communal surfaces and 4.1% of 74 surfaces after conventional terminal disinfection. None of 64 surfaces sampled after HPV decontamination yielded GR-MSSA. Recovery of GR-MSSA from two high level sites suggested that the organism could have been transmitted via air. Occasional

breakdown in hand hygiene compliance and contaminated environmental surfaces probably contributed to transmission.

Introduction

Much attention has been focused on meticillin resistant *Staphylococcus aureus* (MRSA), but meticillin susceptible *S. aureus* (MSSA) remains an important cause of healthcare associated infection, particularly in neonates. Up to 80% of neonates may be colonised with *S. aureus* by day 10 of a stay on a neonatal unit (Denniston and Riordan, 2006; Couto et al, 2007). The profile of colonisation is different from adults, with the most common neonatal sites being umbilical cord, skin, nasopharynx and the gastrointestinal tract (Denniston and Riordan, 2006; Couto et al, 2007). Neonatal patients are particularly vulnerable to bloodstream infection with staphylococci and other hospital bacteria because of their underdeveloped skin and immune systems and requirement for multiple invasive procedures, particularly vascular catheterisation. Infection rates in neonatal units range from six to nine per 1,000 patient days, up to 75% of which are bacteraemias (Denniston and Riordan, 2006; Couto et al, 2007; Curtis and Shetty, 2008).

There have been frequent reports of MSSA outbreaks in neonatal units (Dancer et al., 1990, 1988; Mackenzie et al., 1995; Wilcox et al, 2000). Outbreaks of MRSA are less common (Saiman et al, 2003; Otter and French, 2006; Saunders et al, 2007), probably because of

Table 1. Summary of environmental sampling during the outbreak

	Cohort rooms ¹	Communal areas ²	Post deep cleaning ³	Post HPV decontamination ⁴
Areas sampled	7 bays	–	3 bays	2 bays
No. sites sampled	87	28	74	64
No. sites positive for the outbreak strain (A)	10	2	3	0
%	11.5	7.1	4.1	0.0
Items positive	<i>Direct plating:</i> Monitor (3) Incubator door (2) Nursing bench <i>Enrichment:</i> Incubator door (2) Monitor Floor	<i>Direct plating:</i> Keyboard Ultrasound unit	<i>Direct plating:</i> Monitor High-level light (2)	

¹Eighty-seven environmental sites were sampled from five current and two old cohort bays. Swabs were taken from the catch outside the incubator door or cot side, the touch screen or heart monitor, the computer keyboard, nursing station bench, and the door and floor of each room.

²Twenty-eight communal sites were sampled including mobile ultrasound machines (2), a mobile X-ray machine, the nursing station areas, the blood gas machine, the ultrasound jelly and sites in the milk expressing room.

³Seventy-four sites were sampled in three cohort bays after deep cleaning. Swabs were taken from the catch outside the incubator door or cot side, the touch screen or heart monitor, the computer keyboard, nursing station bench, and the door and floor of each room.

⁴Sixty-four adjacent sites were sampled after HPV decontamination of two cohort-bays.

the relative infrequency of MRSA colonisation in paediatric and maternity patients compared with other groups (Saiman et al. 2003; Otter and French, 2006). Recently, however, neonatal outbreaks with community associated MRSA (CA-MRSA) have highlighted the potential for importation and transmission of community *S. aureus* in this setting (Saiman et al. 2003; Otter and French, 2006). Neonatal *S. aureus* outbreaks may involve contaminated healthcare worker hands or *S. aureus* colonisation (Dancer et al. 1988; Mackenzie et al. 1995; Albrich and Harbarth, 2008), carrier mothers (Behari et al. 2004; Saunders et al. 2007) or contaminated surfaces and equipment (Kaplan et al., 1986; Lejeune et al. 1986; Fujimura et al. 2004).

We describe an outbreak of gentamicin resistant MSSA (GR-MSSA) on our neonatal unit (NNU). The outbreak strain spread rapidly and was more invasive than the background MSSA infection rates for the unit. Investigations identified environmental contamination with the outbreak strain but no colonised staff.

Patients and methods

Setting

Guy's and St Thomas' NHS Foundation Trust is a central London tertiary referral hospital with a 36-bedded NNU. The unit comprises a 12-bed neonatal intensive care unit (NICU) and a 24-bed special care baby unit (SCBU), and receives approximately 800 admissions each year. Approximately 75% are extremely premature or have complex congenital conditions which necessitate prolonged NNU stay. There is a high awareness of the importance of infection control and a dedicated infection control nurse. MRSA and MSSA infections are uncommon on the unit, although there was a small cluster of MRSA colonised babies in 2006 (Otter et al. 2007).

Surveillance of *S. aureus* infections

The infection prevention and control team (IPCT) maintains a daily electronic surveillance system for MRSA and MSSA on the NNU. Results are reviewed daily to identify infections and outbreaks. Once the outbreak was recognised (in November 2007, designated outbreak

month 3), a retrospective analysis of all *S. aureus* isolates identified from carriage and clinical samples, including blood cultures, collected from babies on the NNU from 2002 to 2009 was performed. All isolates of *S. aureus* from the NNU were downloaded from electronic records and gentamicin susceptible (GS)-MSSA, GR-MSSA, MRSA and isolates from the blood were identified.

Patient and staff screening

Staff are not routinely screened for the carriage of MRSA or MSSA. Babies have admission screening swabs from nares, throat and perineum collected for detection of MRSA using selective chromogenic media. These screens do not identify MSSA. During the GR-MSSA outbreak, babies were also routinely screened on admission and weekly (twice weekly from outbreak month 4) for carriage of GR-MSSA in nose, axillae and perineal swabs by culture on blood agar and standard microbiological *S. aureus* identification methods. Clinical samples were collected when infection was suspected. Staff carriage of GR-MSSA was screened by nasal swabbing at the start of each shift in order to determine carriage rather than transient colonisation that may occur during ward work (Albrich and Harbarth, 2008). Parents were not screened. Staff hand-plating was introduced in response to observed breakdowns in hand hygiene compliance to support staff education. In outbreak month 10, we performed a small hand hygiene training exercise. Five-finger hand-impression plates were collected on blood agar before and after hand washing using soap and water for five nurses and three doctors.

Environmental sampling, cleaning and disinfection

Clinical areas in the NNU are routinely cleaned daily by damp dusting all fixtures and fittings and damp mopping the floor with a detergent solution. Terminal disinfection after patient discharge follows a similar regime but includes the use of sodium hypochlorite-containing agents.

A total of 253 environmental surfaces were sampled, including cohort rooms and communal areas before and after cleaning, and cohort rooms before and after hydrogen peroxide vapour (HPV)

Figure 1. Epidemic curve of gentamicin resistant *Staphylococcus aureus* on the neonatal unit. Numbers indicate when the various outbreak interventions were implemented
Key to interventions:

1. Multidisciplinary outbreak team convened. This group reinforced standard infection control procedures and compliance was monitored by the infection control nurse. Staff and equipment were cohorted along with the babies as far as possible. Mothers of colonised babies used cohorted milk expressing equipment at the cot-side. Empirical antibiotic policy for late onset sepsis changed from amoxicillin plus gentamicin to flucloxacillin plus gentamicin. Admission and weekly screening for GR-MSSA introduced
2. All babies on the unit screened for GR-MSSA. Twice weekly screening for GR-MSSA introduced. Environmental screen of the unit performed. Staff screening performed
3. Hand hygiene finger plating exercise performed

decontamination (Table 1). Sterile cotton-tipped swabs moistened in Brain-Heart Infusion (BHI) broth were used to sample environmental surface areas of approximately 25 cm². Swabs were plated onto blood agar both before and after enrichment in BHI broth and *S. aureus* was identified by standard microbiological methods.

In response to initial environmental sampling results, cohort rooms (vacated by affected babies) were decontaminated using HPV (Bioquell, Andover, Hants). HPV decontamination was performed as described by French et al (2004). Briefly, all surfaces were cleaned of visible dirt, HPV equipment was set-up in the room and air conditioning vents and doors were sealed using adhesive tape. Incubators and mobile medical equipment from elsewhere in the unit were moved into the rooms so that they could be decontaminated at the same time. The HPV decontamination process was managed and monitored by Bioquell personnel.

Characterisation of the outbreak strain

S. aureus isolates were identified as detailed above and tested for antimicrobial susceptibility using automated broth micro-dilution (Vitek, bioMérieux, Basingstoke, Hampshire, UK) or disc testing using BSAC methodology. The outbreak strain was identified by gentamicin resistance and all available patient and environmental isolates were characterised by *spa* typing (Harmsen et al, 2003), PCR for the *mecA* gene, pulsed-field gel electrophoresis (PFGE) and toxin gene profiling at the Health Protection Agency's *Staphylococcus* Reference Unit, using methods described by Holmes et al (2005). In addition, DNA microarray-based hybridisation (StaphyType, Alere Technologies, GmbH, Jena, Germany) was performed on selected strains for the simultaneous detection of a range of toxin and antimicrobial resistance genes and species-specific markers (Monecke et al, 2008).

Results

Description of the outbreak

Three neonates had bacteraemia with GR-MSSA during months 1–3 (Figure 1). The outbreak was recognised after the second case of bacteraemia in month 3 (Figure 1). In response, all babies on the unit

were screened. Fifteen further cases, including three bacteraemias and 12 colonised babies were identified by month 8. Five GR-MSSA cases were identified as carriers in month 10 and a further four cases were identified in months 11–14, including one bacteraemia in month 14. No further cases of GR-MSSA were identified on the unit by the time active surveillance ended (December 2009) and no further outbreaks have been identified to date.

A total of 27 cases of GR-MSSA occurred on the unit from months 1–14 (Figure 1). All but the final case had a characteristic antibiogram of resistance to gentamicin with variable penicillin resistance. Twenty two (85%) isolates with the characteristic antibiogram were characterised by *spa* typing and PFGE. Seventeen (77%) belonged to 'strain A' (*spa* t084 and indistinguishable by PFGE) and five to 'strain B' (*spa* t279 and indistinguishable by PFGE). The five strain B isolates occurred in months 10–12. Both *spa* types are associated with isolates belonging to multilocus sequence type clonal complex 15, which is one of the ten dominant lineages of *S. aureus* (Lindsay et al, 2006). The PFGE profiles of strains A and B differed by six bands so were considered 'possibly related' by standard interpretation criteria (Tenover et al, 1995) and *spa* types differed by a single repeat (Table 2). However, differences at several genomic loci were identified based on DNA microarray data, indicating that strain B was not derived directly from strain A (Table 2). Both strains A and B lacked all tested virulence factors including Pantone-Valentine leukocidin, enterotoxins A-E and G-J; toxic shock syndrome toxin-1; and epidermolytic toxins A, B and D.

Ten (59%) patients were carriers only; seven (41%) patients with strain A had positive clinical specimens, including six patients (35%) with bacteraemia. Five of six bacteraemias were related to intravascular catheters. The outbreak strain was associated with a high rate of bacteraemia compared with gentamicin susceptible *S. aureus*: from 2002 to 2009, 28 (10%) of 284 patients with gentamicin susceptible *S. aureus* had one or more episodes of bacteraemia, compared with six (35%) of the 17 strain A patients ($p=0.007$, Fisher's exact test).

Retrospective analysis indicated that GR-MSSA was uncommon on the unit, with only two cases reported during 2002–2005. Thirteen

Table 2. Summary of key genes identified in a representative isolate from clones A and B

Gene	Function	Location	Clone A ¹	Clone B ²
<i>blaZ</i>	β -lactamase (penicillin) resistance	Mobile genetic element	–	+
<i>aacA_aphD</i>	Aminoglycoside (gentamicin/tobramycin) resistance	Mobile genetic element	+	+
<i>aphA_3</i>	Aminoglycoside (tobramycin/neomycin) resistance	Mobile genetic element	–	+
<i>Sat</i>	Streptothricin resistance	Mobile genetic element	–	+
<i>qacA</i>	Efflux pump	Mobile genetic element	+	–
<i>fosB – plasmid³</i>	Fosfomycin resistance	Mobile genetic element	+	–
<i>fosB</i>	Fosfomycin resistance	Genomic	+	+
<i>Hlb</i>	β -haemolysin	Genomic	–	+
<i>sak</i>	Staphylokinase	Genomic	–	+
<i>splE</i>	Serine protease E	Genomic	+	–
<i>set 6</i>	Staphylococcal antigen-like protein	Genomic	+	–
<i>ssl 1-9</i>	Staphylococcal antigen-like proteins	Genomic	+	–

¹spa t084, repeat profile 07-23-12-34-34-12-12-23-02-12-23

²spa t279, repeat profile 07-23-12-34-34-34-12-12-23-02-12-23.

³The DNA hybridisation array includes separate probes for variants of genomic or plasmid encoded fosB.

Figure 2. Secular trend in annual number of patients with any *Staphylococcus aureus* positive culture on the neonatal unit between 2002 and 2009

GR-MSSA = gentamicin resistant, methicillin-susceptible *S. aureus*

GS-MSSA = gentamicin susceptible, methicillin-susceptible *S. aureus*

MRSA = methicillin resistant *S. aureus*

cases occurred between April 2006 and April 2007 (Figure 2). Six of these shared the characteristic antibiogram of the outbreak strain. However, the last of these cases in March 2007 had a distinct *spa* type (t9731) from the outbreak strain so was not considered related.

Outbreak interventions

A multidisciplinary outbreak group was convened when the outbreak was recognised. This group reinforced standard infection control procedures and Trust guidance around line care, including best practice regarding line insertion and maintenance. Compliance was monitored by the infection control nurse and neonatal unit infection control link nurses. Staff and equipment were cohorted along with the babies as far as possible. Colonised and non-colonised babies were fed at the cot-side including the use of disposable breast pumps. Empirical antibiotic policy for late onset sepsis changed from amoxicillin plus gentamicin to flucloxacillin plus gentamicin. The unit remained open to admissions throughout the outbreak.

Staff and environmental screening

Out of 125 staff members handling babies, 113 (90%) were screened for carriage of GR-MSSA, but no staff carriers were identified.

The staff hand-plating showed similar levels of hand contamination with mixed bacterial species before and after hand washing. This

information, and the associated photographs of the agar plates, were used to encourage improvements in staff hand decontamination.

Fifteen (7.9%) of 189 sites sampled before HPV decontamination were contaminated with the outbreak strain A (Table 1). The highest proportion of positive samples (11.5%) was identified in the bays used to cohort colonised and infected neonates. The outbreak strain was isolated from one keyboard in the nursing station and one touch panel on the mobile ultrasound unit, which represented 7.1% of samples taken in communal areas. Deep cleaning of cohort rooms following the discharge of affected babies reduced the frequency of contamination to 4.1% but the outbreak strain was cultured by direct plating from a bedside monitor and from two high level light fittings. The two positive culture sites on the light fittings were on upper surfaces of equipment mounts, close to the ceiling and beyond the standard reach of cleaners. These surfaces were heavily coated with dust, suggesting that they had not been touched since installation. The isolation of the outbreak strain from these high surfaces is interpreted as evidence of airborne spread of contamination. None of the sites sampled following HPV decontamination yielded the outbreak strain.

Discussion

Advances in neonatal intensive care have led to a growing population of low birth weight, low gestational age infants who are at great risk of acquiring infections (Denniston and Riordan, 2006; Couto et al, 2007; Zingg et al, 2008). Studies of *S. aureus* outbreaks have identified several possible routes and sources of transmission, including staff hands, staff carrier(s), the contaminated environment, air or equipment, via mother-baby contact or contamination of feeds during milk expression or feeding (Otter and French, 2009; Kaplan et al, 1986; Lejeune et al, 1986; Dancer et al, 1988; Mackenzie et al., 1995; Behari et al, 2004; Fujimura et al, 2004; Albrich and Harbarth, 2008). We investigated several possible routes of transmission. No staff carriers were identified, although 10% of staff were not screened and screening is not 100% sensitive, so we cannot rule out the involvement of staff carriers. We did, however, identify breakdowns in hand hygiene by a hand plating exercise. Given the high frequency of contact between healthcare workers' hands and neonates and their immediate surroundings on NNUs (Cohen et al, 2003), it seems likely that some of the transmission during our outbreak was due to inadequate hand hygiene.

In a previous outbreak on our NNU, 17% of 48 surfaces were contaminated with MRSA, including two sites in the communal milk expressing room (Otter et al, 2007). Studies have identified environmental contamination during other outbreaks on NNUs (Lejeune et al, 1986; Kaplan et al, 1986; Fujimura et al, 2004). For example, 8% of 141 samples from surfaces and air were contaminated with epidermolytic toxin-producing epidemic *S. aureus* strains during an American outbreak (Kaplan et al, 1986). Other studies have not identified a significant environmental reservoir for NNU outbreaks despite extensive sampling (Farrington et al, 1990). In the present study we identified environmental contamination with the outbreak strain on 11.5% of surfaces in cohort rooms, 7.1% of communal sites and 4.1% of surfaces in cohort rooms that had been deep cleaned. We found the outbreak strain on two high level surfaces that probably had not been touched since installation, indicating that airborne environmental spread had occurred, but we do not know if air contributed to transmission to patients.

We did not identify any contamination with MRSA on the unit and no *S. aureus* was identified on surfaces in the milk expressing room, unlike the findings in our previous environmental survey on this unit (Otter et al, 2007). A new disinfection regimen was introduced in the milk expressing room following the 2006 MRSA outbreak (Otter et al, 2007), and in the current outbreak, mothers of affected neonates expressed milk at the bedside to prevent contamination in the milk expressing room. However, the contamination at communal sites could have contributed to the continuation of the outbreak. Deep cleaning failed to eradicate the outbreak strain whereas HPV decontamination did, confirming the effectiveness of HPV environmental decontamination reported in other studies, including an outbreak of *Serratia marcescens* on an NNU (Bates and Pearse, 2005; Jeanes et al, 2005).

The outbreak strain had variable resistance to penicillin, which was probably associated with unstable plasmid-encoded penicillinase production (Lacey, 1975). The outbreak strain resulted in significantly more bacteraemia episodes than GS-MSSA. Most individuals who carry *S. aureus* do not develop disease and it seems that invasive disease is the result of a complex interplay between bacterial, host and ecological factors (Lindsay and Holden, 2006). Five of six bacteraemias due to the outbreak strain were catheter-associated so we cannot discount the possibility that the high proportion of bacteraemias caused during the outbreak was due to invasive procedures alone, and we had not implemented line-care bundles at the time of the outbreak. The outbreak strain did not possess any known virulence factors, but a recent outbreak of the ST239 'TW' MRSA

strain on our adult intensive care unit illustrates that certain *S. aureus* strains have a propensity for invasive disease so further investigation of the outbreak strain to seek new virulence factors and/or markers of 'fitness' may be warranted (Edgeworth et al, 2007).

An unusually high prevalence of GR-MSSA was noted on the unit for approximately 12 months before and after the outbreak. Based on the variable antibiograms of these strains and more detailed typing of the later isolates, we attribute this to repeated introduction and spread of a small number of different GR-MSSA clones within the unit. The small cluster of cases that occurred in months 10–12 was caused by a related but distinct *S. aureus* strain.

In summary, this outbreak is consistent with the notion that some strains of *S. aureus* have an increased capability to cause outbreaks and cause invasive disease in an ICU setting (Edgeworth et al, 2007). In this outbreak, the strain spread rapidly and was associated with a high rate of invasive disease, but further work is needed to identify possible bacterial factors associated with this. Although we were alerted to the presence of this strain by the distinctive gentamicin resistance marker, confirmation of outbreak strains requires molecular typing because antibiograms alone do not identify clonal spread. Some transmission was probably due to breakdowns in hand hygiene practice and environmental contamination. The recovery of the outbreak strain from very high surfaces and continuing contamination of surfaces before and after deep cleaning suggests that air contamination may have been involved in environmental transmission. Our outbreak was terminated effectively by strict enforcement of hygienic practices, patient isolation/cohorting and environmental decontamination by HPV.

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Declaration of conflicting interest

JAO is employed part-time by Bioquell (UK) Ltd. All other authors report no potential conflicts of interest.

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