Outbreak of clonal complex 22 Panton–Valentine leucocidin-positive methicillin-resistant *Staphylococcus aureus*

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Abstract

Aims: We describe the investigation and control of a nosocomial outbreak of Sequence Type (ST) 22 MRSA containing the Panton–Valentine leucocidin (PVL) toxin in an acute multispecialty surgical ward at University Hospital Birmingham NHS Foundation Trust.

Methods: A patient was classed as acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) if they had a negative admission screen and then had MRSA isolated from a subsequent screen or clinical specimen. Spa typing and pulsed field gel electrophoresis (PFGE) was undertaken to confirm MRSA acquisitions.

Findings: The Infection Prevention and Control Team were alerted to the possibility of an outbreak when two patients acquired MRSA while being on the same ward. In total, five patients were involved in the outbreak where four patients acquired the PVL-MRSA clone from an index patient due to inadequate infection control practice. Two patients who acquired the strain developed a bloodstream infection. Infection control measures included decolonisation of affected patients, screening of all patients on the ward, environmental sampling and enhanced cleaning.

Discussion: Our study highlights the potential risk of spread and pathogenicity of this clone in the healthcare setting. Spa typing and PFGE assisted with confirmation of the outbreak and implementation of infection control measures. In outbreaks, microbiological typing should be undertaken as a matter of course as without specialist typing identification of the described outbreak would have been delayed.

Keywords

Methicillin-resistant *Staphylococcus aureus*, outbreak, Panton–Valentine leucocidin, urology setting

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Introduction

Staphylococcus aureus is a major cause of health-care associated infections worldwide (Cookson et al., 2007; Garvey et al., 2016b). Despite the recent decline in incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in several European countries, infection remains a major cause of avoidable morbidity and mortality in patients admitted to hospital (Garvey et al., 2016b; Robotham et al., 2011; Simor and Loeb 2009).

Panton–Valentine leucocidin-positive MRSA (PVL-MRSA) has emerged to become a global cause of community-acquired (CA) infections and subsequently of sporadic nosocomial outbreaks (Teare et al., 2010). PVL is a pore-forming toxin which causes lysis of granulocytes and

monocytes as well as tissue necrosis (Shore et al., 2014). PVL is encoded by two genes, lukF-PV and lukS-PV, that are encoded on a range of different lysogenic bacteriophages (Shore et al., 2014). While outbreaks of PVL-producing

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methicillin-sensitive *S. aureus* (MSSA) were reported in the 1950s and 1960s, it was in the 1990s when PVL was first reported in newly emerging CA-MRSA strains (Holmes et al., 2005). Most PVL *S. aureus* infections have been limited to localised skin and soft tissues but a minority have resulted in a fatal outcome, typically in a context of necrotising pneumonia or fasciitis (Ali et al., 2012; Ellington et al., 2010).

In the UK, genes encoding for PVL have been estimated to be carried in less than 2% of clinical isolates of *S. aureus* whether methicillin-sensitive or -resistant (Holmes et al., 2005; Shallcross et al., 2010). Reference laboratories only receive a small number of selected isolates so this is likely to under estimate the true burden of the disease (Holmes et al., 2005; Shallcross et al., 2010). In England, the majority of PVL-positive strains have been MSSA (Holmes et al., 2005; Shallcross et al., 2010). Outbreaks of PVL *S. aureus* in both community and healthcare settings have attracted high-profile media attention and prompted concern regarding the transmissibility and virulence sometimes associated with these organisms (Ali et al., 2012; Patel et al., 2013). PVL-positive strains of *S. aureus* usually cause superficial skin and soft-tissue infections (including abscesses and pustules) in otherwise healthy individuals, but can cause potentially fatal necrotising pneumonia or necrotising fasciitis (Teare et al., 2010). Although PVL-positive strains of *S. aureus* are more commonly identified in individuals in the community than in hospital, once it is brought into a hospital environment it can spread (Otter and French, 2006; Watkins et al., 2012). In the UK, there have been several reports of PVL-MRSA outbreaks in a hospital setting such as paediatric neonatal, intensive care and burns unit (Ali et al., 2012; Orendi et al., 2010; Patel et al., 2013; Shallcross et al., 2010; Teare et al., 2010). Transmission of PVL-MRSA has been controlled with implementation of multiple infection prevention measures (Patel et al., 2013).

Here, we describe the investigation and control of a nosocomial outbreak of ST 22 MRSA containing the PVL toxin, in an acute multispecialty surgical ward including urology, maxillofacial surgery and trauma at University Hospitals Birmingham (UHB) NHS Foundation Trust. The Infection Prevention and Control Team (IPCT) were alerted to the possibility of an outbreak when we identified two MRSA acquisitions on the same ward. The outbreak involved five patients, two of whom developed a blood stream infection; the remaining three patients were colonised.

Materials and methods

Setting

UHB is a teaching hospital in Birmingham which provides clinical services to nearly 1 million patients every year. The outbreak occurred on an acute multispecialty surgical ward including urology, maxillofacial surgery and trauma at UHB comprising 36 beds, 16 of which are side rooms.

MRSA patient screening

MRSA screening of all patients admitted to UHB is standard practice. Swabs are taken from the nose, groin and throat as well as any wounds or sites of indwelling devices. Inpatients with more than 28 days' stay are rescreened. Enhanced screening was undertaken during the outbreak and involved all patients on the ward being screened for MRSA weekly during the outbreak and four weeks after the last transmission.

Laboratory screening

MRSA screening swabs were directly plated on to Chromogenic agar (bioMérieux, Marcy l'Etoile, France) and incubated at 37°C in air for 18–24 h. Presumptive MRSA isolates were identified biochemically on the Vitek 2 Systems (bioMérieux, Marcy l'Etoile, France), latex agglutination (Staph Latex Kit, Pro-Lab Diagnostics, Bromborough, UK) and DNase Test Agar (Thermo Fisher Scientific, Loughborough, UK). Antibiotic susceptibility was performed by Vitek 2 Systems (bioMérieux, Marcy l'Etoile, France).

Clinical samples

All clinical specimens were cultured using standard laboratory investigations (SMI B29).

Molecular characterisation of MRSA

MRSA was characterised by the national Staphylococcus Reference Unit (Microbiology Services Colindale, Public Health England, London, UK). The presence of PVL was confirmed by polymerase chain reaction (PCR) and the strains characterised by spa typing, pulsed field gel electrophoresis (PFGE) and variable number tandem repeat (VNTR). Whole genome sequencing (WGS) was used to confirm the relatedness of the PVL-MRSA strains. This was undertaken by the Institute of Microbiology and Infection at the University of Birmingham. Spa typing is undertaken on all MRSA patient acquisitions at UHB.

MRSA acquisitions

A patient was classed as acquiring MRSA if they had a negative admission screen and then MRSA isolated from a subsequent screen or clinical specimen, 48 h after admission.

Case definition

A case was defined as a patient from whom ST 22 PVL MRSA, spa type 852 was isolated.

Identification of possible linked cases

Spa typing enables the IPCT to identify any possible transmission events and clusters throughout the Trust. Using this

routine surveillance, the infection control team was alerted to the possibility of an outbreak when spa typing revealed two patients had the same strain of PVL-MRSA. The last reported MRSA acquisition on this ward was over one year before this current outbreak. During the next five months, a further three patients acquired an indistinguishable strain via spa typing, PFGE, VNTR and WGS.

Outbreak Control Team (OCT)

An OCT was convened comprising representatives from the Trust (IPCT), Director of Infection Prevention and Control (DIPC), senior Urology medical and nursing staff, Public Health England (PHE) Consultant in Communicable Disease and Control (CCDC), a member of the compliance team and members of the facilities staff. Outbreak management was based on national guidance for communicable diseases and expert knowledge of the outbreak team (Communicable Disease Outbreak Management, 2014).

Decolonisation of MRSA-positive cases

A decolonisation course was commenced for patients colonised with MRSA. This involved 2% mupirocin nasal ointment three times a day to both nostrils for a total of five days and daily octenisan (Schulke and Mayr UK Ltd) body-wash applied as a liquid soap directly on to the skin for the duration of the patient stay. No rescreening was performed while the patient was on decolonisation treatment, unless for specific reasons such as a long-stay patient or clinical need. The average length of stay for patients at UHB is four days.

Environmental swabbing

Environmental sampling was carried out on multiple macroscopically clean touch-points throughout the ward including such areas as the patient's bed and mattress, and door handles and bed tables. MW729 Polywipe™ sponges (Medical Wire & Equipment) were used to sample environmental surfaces using the protocol described by Garvey et al., 2016a.

Staff screening

After the fourth case it was decided to screen staff with skin complaints, such as boils or eczema, to identify if any healthcare workers were harbouring the PVL-MRSA clone. Swabs were taken from the nose, groin and throat as well as any wounds of the staff. All swabs were processed as described above.

Results

The outbreak ward

The IPCT were alerted to two patients having acquired MRSA on an acute multispecialty surgical ward including

urology, maxillofacial surgery and trauma. The ward was staffed by ten nurses per shift with 12,140 bed days/year, with an average length of stay of 1.9 days for patients.

Case description

The index patient was admitted from another Trust for trauma surgery (Table 1) and spent two days on the outbreak ward (Figure 1). The patient had no previous history of admission to the Trust. A wound swab taken on admission was positive for MRSA, the result being known after the patient was discharged.

Patient 1 was admitted from another Trust following postoperative complications for a urological problem (Table 1). Patient 1 also had a second admission to the ward soon after discharge, again for postoperative complications; this admission screen was positive for MRSA (Figure 1). Results of the admission screen were not available until after patient 1 was discharged. The patient had no previous admissions to the Trust.

Patient 2 was admitted for an elective urological procedure (Table 1). The patient was discharged for one day and readmitted as an emergency with query infection (Figure 1). The patient had multiple visits to UHB, the last visit to the outbreak ward being one year previously. During implementation of the weekly MRSA screens this patient was found to be MRSA-positive.

Patient 3 was admitted for an elective urological surgery (Table 1). The patient was a longstanding patient with multiple co-morbidities with previous admissions to the Trust; this patient's last visit to the outbreak ward was two years previously. Patient 3 was identified as being positive as part of the weekly MRSA screens; however, the patient was also found to have a skin and soft-tissue infection which was the source of an MRSA bacteraemia.

Patient 4 was an elective urological admission to UHB (Table 1). The patient had multiple admissions to UHB with the last admission to the outbreak ward being six months previously. Patient 4 was admitted to the outbreak ward on day 95 for nine days (Figure 1); however, the patient missed the weekly MRSA screens during this period. On day 143, patient 4 was readmitted to the Trust onto a different ward due to a respiratory infection (Figure 1). An MRSA screen on this admission was positive for MRSA.

On examination of the cases all but one of the patients had surgery at UHB. Three of the patients had urological surgery; however, these were never in the same time period or in the same theatre so this was ruled out as a source of cross-transmission. None of the patients had the same procedures. The only commonality was presence on the same ward during the period of the outbreak. Three of the patients showed signs of infection with MRSA: the index patient and patients 3 and 4. The index patient and patient 3 had skin and soft-tissue infections with MRSA which is

Table 1. Description of five cases of colonisation or infection with hospital acquired ST 22 PVL MRSA, spa type t852.

Case	Description of cases	Management/ Infection control
Index	Admitted from another Trust for surgery on a flexor sheath infection of the thumb.	MRSA screen negative. Patient not isolated as not known to be MRSA-positive. Left thumb wound debridement and removal of foreign body on admission, wound-cultured MRSA, MRSA infection in wound. Patient treated with antibiotics after discharge. Patient thought to be admitted with MRSA.
Patient 1	Admitted from another Trust after having postoperative complications for a radical retropubic prostatectomy. Second admission emergency postoperative complications.	MRSA screen negative on first admission. MRSA screen positive for MRSA on second admission; result not known till discharge, no clinical signs of infection. Thought to acquire MRSA during first admission, was located in the same bay as index patient. Patient never isolated during both admissions as short admissions and not known to be colonised with MRSA.
Patient 2	First admission admitted for elective surgery endoscopic resection of a bladder tumour. Second admission emergency with urosepsis and pulmonary oedema.	MRSA screen negative on first admission. Second admission MRSA screen negative, during inpatient stay day 76 of outbreak positive MRSA screen, decolonisation regime commenced, no clinical signs of infection, isolated when MRSA result known. During second admission was in same bay as patient 1 for three days.
Patient 3	Admitted for elective surgery, laparotomy for urinary diversion with ileal conduit formation.	Patient always isolated. Complicated patient with multiple co-morbidities. During inpatient stay developed pancreatitis, chest infections and cellulitis. All treated with antibiotics. Patient developed an MRSA bacteraemia likely skin and soft-tissue source which was treated with antibiotics. MRSA inpatient screen positive on day 76 of outbreak.
Patient 4	Patient admitted for elective surgery for cystoscopy, left retrograde study and left ureteroscopy; for bilateral hydronephrosis and suspicious lesion at left upper pole calyx. Readmitted twice more as an emergency for CAP and urosepsis.	MRSA screen negative on first admission, missed weekly inpatient screen on Urology ward, patient always isolated. Admitted to a respiratory ward on second admission, MRSA screen negative, patient always isolated due to Influenza A infection. Developed CAP which was treated with antibiotics. MRSA inpatient screen positive for MRSA, decolonisation regime, no signs of infection. After discharge for CAP represented to the Trust with sepsis an MRSA bacteraemia secondary to a UTI treated with antibiotics.

CAP = Community acquired pneumonia; UTI = Urinary tract infection.

indicative of PVL infection; however, patient 4 showed no PVL-like infection. Interestingly, patients 3 and 4 developed an MRSA bacteraemia (Table 1). Patients 3 and 4 had prolonged hospital stay due to their MRSA infection/bacteraemia; they also had multiple co-morbidities and were aged >65 years compared with the other three patients. All the patients with infections were treated with antimicrobials.

Outbreak control measures

Typing results on the acquired MRSA strain by patient 1 revealed this was the same strain as the index patient. This result was reported ten days after admission of patient 1 (Figure 1). At this point, an OCT was convened. As both patients were located on the same ward, multiple infection prevention measures were implemented after this result to try to prevent further transmission (Figure 1). In line with UHB policy, the patients with MRSA were nursed in a single room. Standard precautions are undertaken, consisting of correct hand hygiene based on the five moments of hand

hygiene, the use of gloves and apron when in direct contact with patients, for any procedures involving bodily fluids and contact with the patient's environment (Pittet et al., 2000). During days 70–75, all staff with skin complaints/conditions were screened by the Occupational Health Department for MRSA (Figure 1). A total of four staff were screened and all were negative. Enhanced hand-hygiene awareness, including teaching sessions to all staff groups, were implemented on the ward from day 70 onwards (Figure 1). Audits undertaken on day 70 of the outbreak revealed 48% hand-hygiene compliance. After educational sessions, hand-hygiene compliance rose to 72% and by the end of the outbreak period hand-hygiene compliance improved to 89%. In addition, on day 76, weekly MRSA screening was commenced for all inpatients on the ward equating to 36 patients. Patients 2 and 3 were identified as part of this initiative during the first round of screening (Figure 1). Due to the continued outbreak, local infection control training session updates for all the ward staff including medical and peripartetic teams were undertaken.

Figure 1. Timeline of patients who acquired the PVL-MRSA outbreak strain, with selected infection control interventions.

Key: Square shape represents first PVL-MRSA-positive specimen. Patients 1 and 2 had two admissions to the urology ward during the outbreak. Patient 4 had three admissions to the Trust, the first admission was to the urology ward, the second admission to a respiratory ward and the third admission to a General Medicine ward.

In response to the further two patients acquiring MRSA, enhanced environmental sampling of the outbreak ward was undertaken on day 80 (Figure 1) to identify if the environment was contaminated with MRSA and contributing to the ongoing transmission. MRSA was isolated from the environments close to the colonised patients. Out of the 40 environmental samples undertaken, 16 were positive for MRSA. Molecular typing revealed these isolates were the outbreak strain. The outbreak ward at UHB normally receives a standard clean consisting of damp dusting the ward with a detergent (Sprint Multiuso, Diversey); toilets are cleaned with a sanitary cleaner (Sani Cid, Diversey); floor cleaning with a floor cleaner (Jontec 300, Diversey). Bed spaces where patients are discharged with no known infections or diarrhoea are cleaned using detergent wipes (Clinell, Universal wipes). In light of the environmental swabbing results, enhanced daily disinfection of the ward environment with a hypochlorite solution/ detergent (1000 ppm; Chlor Clean) was instigated (Garvey et al., 2016a). Deep cleaning for all affected rooms on patient discharge including bays was also implemented. This included cleaning and disinfection with a hypochlorite solution/detergent (1000 ppm; Chlor Clean) followed by hydrogen peroxide misting (Oxypharm) at a concentration of 6% (Garvey et al., 2016a). During the enhanced cleaning, environmental sampling was again undertaken. Of the 40 samples

taken, six (15%) were positive for MRSA. MRSA was again isolated in areas close to the colonised patients.

Towards the end of the outbreak, on day 130 a fourth patient was positive for MRSA; however, the patient was on a different ward at this time (Figure 1). Typing revealed this strain was indistinguishable from the outbreak strain and detailed epidemiology of the patient identified the patient had been on the outbreak ward on day 96 of the outbreak (Figure 1).

After the last positive PVL-MRSA patient involved in the outbreak was discharged from the ward, no further cases have been identified during the 12-month follow-up.

Characterisation of isolates

All isolates were ST 22 MRSA, spa t852, SCCmecIV distinct to that of EMRSA-15 (personal communication with Professor Angela Kearns), agr group 1 and PVL-positive. They were indistinguishable by PFGE, VNTR, spa typing and were all identical to each other by WGS with no Single Nucleotide Polymorphisms (SNPs). Patient 3 had two strains of MRSA, both spa type t852; however, the isolate from the screen was negative by PCR for PVL while the blood culture isolate was positive for PVL. The five PVL-MRSA isolates were resistant to erythromycin, ciprofloxacin and clindamycin, but susceptible to gentamicin,

vancomycin, linezolid, teicoplanin, fusidic acid, rifampicin and trimethoprim. The strains were all sensitive to mupirocin.

Discussion

Multiple strains of PVL-MRSA have been documented in the UK and there has been a reliance on the use of antibiograms such as quinolone susceptibility for presumptive isolation of such strains. For this outbreak, using the antibiogram alone to identify PVL-MRSA would have missed this strain due to antibiotic susceptibility of the outbreak strain being indistinguishable from the predominant HA-MRSA strain prevalent at UHB (data not shown) (Patel et al., 2013). The predominant healthcare-associated MRSA strain in the UK and at UHB is EMRSA 15, CC22- SCCmecIVc, spa type t032. Both t032 and the outbreak strain ST 22 PVL MRSA, t852 were resistant to erythromycin, clindamycin and ciprofloxacin; making it difficult to identify the outbreak strain without molecular typing (Ali et al., 2012; Holmes et al., 2005; Teare et al., 2010). In addition, symptoms indicative of PVL-MRSA including boils or SSTIs would not have been a marker of PVL-MRSA in this outbreak as four of the surgical patients did not have these conditions (Ali et al., 2012; Holmes et al., 2005; Teare et al., 2010).

Control measures for MRSA have mainly relied upon the identification and isolation of colonised and infected patients to prevent them as acting as a reservoir of infection and onward transmission (Hardy et al., 2007). Outbreak-provoking factors identified included the admission of a patient who was not recognised as being colonised with MRSA and not immediately isolated. Deficiencies identified in infection prevention and control practice included poor hand and environmental hygiene. We hypothesise that the unknown MRSA status of the index patient on admission led to the organism being disseminated in the environment and potential transmission to other patients not detected in the current investigation. In addition, a failure to isolate has probably led to the exposure of patients in the bay of the index patient and this has also contributed to transmission. There were times when no patients were positive for MRSA on the ward; as such one cannot rule out the organism was transmitted to others who were missed in the outbreak or that there was transient colonisation of staff. Ward hand-hygiene audits during the outbreak were low at 48%. In addition, the environment was heavily contaminated with MRSA which would have aided transmission of MRSA around the ward. It is not uncommon for hand hygiene and the environment to play a role in the transmission of MRSA in a hospital setting; various reports in the literature have detailed these transmission routes previously (Hardy et al., 2007). As with all outbreaks, this paper highlights the importance of transmission based precautions when dealing with a patient colonised with MRSA including

side room isolation, appropriate hand hygiene and correct use of gloves and aprons. The greater the proportion of hand-hygiene opportunities taken the fewer opportunities for cross-transmission (Pittet et al., 2000). Increased hand-hygiene audits and teaching helped with preventing the transmission of MRSA on the outbreak ward, this paper also shows the importance of frequent hand-hygiene audits in the absence of cross-transmission, to optimise and prevent outbreaks.

At UHB all MRSA acquisitions are molecular typed to identify transmission events, the use of typing readily identified the PVL-MRSA strain not seen previously at UHB. Molecular typing, primarily spa typing and VNTR, led to the rapid implementation of infection control measures to reduce the transmission of this strain in the current setting. Spa typing and VNTR both identified the PVL-MRSA strain in this outbreak; WGS was later used to determine the relatedness of the isolates and no SNPs could be identified between the strains (data not shown). It must be noted there are time constraints waiting for the results of typing if relying solely on this for outbreak identification.

Once identified, control of this outbreak was rapidly established using infection control measures implemented by a OCT. However, the continued presence of patients with the outbreak strain on the ward necessitated the prolonged implementation of control measures and the monitoring of their implementation. Actions included isolation of affected patients into side rooms, regular weekly screening of ward patients, screening of staff with any skin and soft tissue conditions, teaching around hand hygiene, daily hand-hygiene audits, screening of the ward environment with enhanced cleaning of the ward. MRSA can survive for more 175 days on a ward. In addition, once MRSA has been eradicated from the environment rapid recontamination can occur within 24 h (Hardy et al., 2007). This demonstrates that environmental recontamination occurs despite daily cleaning with standard methods. In the current study, the PVL-MRSA outbreak strain was found in the environment in up to 40% of the areas environmental sampled. Enhanced cleaning reduced the bioburden considerably in the environment; however, it did not eliminate the strain completely. Even with enhanced cleaning and environmental disinfection, while colonised patients remained on the ward, environmental samples were frequently positive. PVL outbreaks can persist in the healthcare setting (Ali et al., 2012; Holmes et al., 2005; Teare et al., 2010) without identification through microbiological typing, and without several infection control measures this outbreak could have continued beyond the six-month period. The outbreak involved five patients over a five-month period, which was a relatively small number of patients in light of the heavy environmental contamination and poor hand-hygiene compliance. The strain could be considered a 'slow spreader', and without microbiological typing of MRSA acquisitions,

this strain and the subsequent outbreak would have been difficult to detect.

Our study highlights the potential risk of spread of this clone in the healthcare setting and the seriousness of PVL infections in relation to the two bacteraemias seen. All MRSA colonisation acquisitions at UHB are routinely sent for typing, without which we would not have identified / recognised the outbreak as quickly. Molecular typing of all hospital MRSA acquisitions should be considered as a tool in active surveillance and outbreak situations, aiding infection prevention and control measures.

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