Clinical, molecular and epidemiological description of a cluster of community-associated methicillin-resistant *Staphylococcus aureus* isolates from injecting drug users with bacteraemia

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Abstract

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is an increasing problem, predominantly in previously healthy individuals including notable risk groups such as the homeless, those who play close-contact sports, military personnel, men who have sex with men (MSM) and injecting drug users (IDUs). Over a 5-month period, four IDUs were admitted to Addenbrooke's Hospital, Cambridge, UK, with MRSA bacteraemia. All four patients presented with complex clinical features, with more than one focus of infection, and were linked epidemiologically. The atypical antibiogram of the MRSA isolates (ciprofloxacin-susceptible) prompted further characterization, both phenotypically (antibiotic resistance typing; phage typing) and genotypically (detection of toxin genes by PCR; pulsed-field gel electrophoresis (PFGE); Staphylococcal chromosome cassette (SCC) *mec* typing; multi-locus sequence typing (MLST)). All four isolates had similar antibiograms, were Panton-Valentine Leucocidin (PVL) toxin gene-negative, harboured SCC*mec* type IV and were closely related as shown by phage typing and PFGE. These isolates were representatives of a community-associated clone, ST1-MRSA-IV, known to be circulating in IDUs in the UK since 2001. This paper presents a detailed description of the clinical, microbiological and epidemiological features of a series of CA-MRSA bacteraemias in IDUs in the UK.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a pathogen of key microbiological and public health significance, and is becoming increasingly important in the community. Community-associated MRSA (CA-MRSA) first appeared about two decades ago and tended to affect previously healthy individuals, with clusters occurring among specific population groups such as military recruits and sports team players. Over the past few years, other high-risk groups have been identified, such as men who have sex with men [1], people in jail [2], the district nurse patient population [3], injecting drug users (IDUs) [4] and the homeless [5]. Alarmingly, CA-MRSA is now increasingly recognized outside these patient groups, and the current estimates of prevalence in the UK general population are between <0.1% and 1.5% [6,7].

Epidemiological characteristics of patients with CA-MRSA infections are similar to those of patients with CA-methicillin-susceptible *S. aureus* (MSSA) infections [8] but, at the molecular level, CA-MRSA strains are different from healthcare-associated MRSA [9]. They tend to be more susceptible to non-β-lactam agents, carry smaller staphylococcal chromosome cassette (SCC) *mec* types (usually type IV or V) and often harbour the genes encoding the Panton-Valentine leucocidin (PVL) virulence factor. Two clones (USA300 and USA400) harbouring SCC*mec* type IVa and PVL are found over a wide geographical area in the USA [10]. These American clones are not yet common in the

UK or elsewhere in Europe. In contrast, a specific clone which does not encode the PVL toxin is circulating among the IDU population in England and Wales. This was first apparent at the beginning of the millenium and continues to be reported [11–13]. We describe the clinical, microbiological and epidemiological features of four such isolates, collected over a 5-month period (October 2006–February 2007), from cases of bacteraemia at Addenbrooke's Hospital, Cambridge, UK.

Materials and Methods

The clinical case notes of the individual patients were reviewed. Blood cultures were processed using the BacT-Alert system (bioMérieux, Basingstoke, UK) in the Clinical Microbiology and Public Health Laboratory, Health Protection Agency, Addenbrooke's Hospital, Cambridge, UK. Initial characterization of MRSA was performed according to National Standard Methods (http://www.hpa-standardmethods.org.uk/documents/bsop/pdf/bsop29.pdf).

Phenotypic characterization of MRSA isolates

Methicillin susceptibility was determined using oxacillin strips on salt agar. Other antibiotic susceptibility testing (R-type) was performed in the diagnostic laboratory according to the British Society of Antimicrobial Chemotherapy (BSAC) method [14], and confirmed by the Antibiotic Resistance Evaluation Unit (HPA, Colindale, London) using agar dilution for the determination of minimum inhibitory concentrations (MIC) [14]. Phage typing was performed as described previously [15].

Genotypic characterization of MRSA isolates

Genotypic characterization included detection of toxin genes by PCR, pulsed-field gel electrophoresis (PFGE), SCC*mec* typing and multi-locus sequence typing (MLST). All MRSA isolates were screened for 14 staphylococcal toxin genes: enterotoxins A–E and G–J, exfoliative toxins A, B and D, toxic shock syndrome toxin-1 and PVL [15]. *mecA* testing was performed as described previously [15]. PFGE of *Sma*I-digested DNA was performed at the Staphylococcus Reference Unit according to standard protocol [15]. The control strains were EMRSA-15 variant B1, and a representative of the MRSA clone previously identified in IDUs in the UK (isolated in a city other than Cambridge in 2006). Further typing was performed using multiplex PCR according to the protocols of Zhang [16] for Class A/Class B *mec* and Hanssen [28] for *ccr* gene complex. MLST was performed as described by Enright [17], and sequence type (ST) assignment was based on the sequence of the alleles at each locus of seven housekeeping genes, using the MLST database (http://www.mlst.net).

Results

Over a 5-month period, four cases of bacteraemia as a result of MRSA with an unusual antibiogram (susceptible to ciprofloxacin and resistant to erythromycin and fusidic acid) were seen in IDUs admitted to our hospital. The clinical cases are given below.

Case A

Case A as a 24-year-old HIV-negative Caucasian male who presented in February 2007 with a short history of rigors, sweating, painful legs and haemoptysis. He was a known heroin injector and had a history of deep vein thrombosis (DVT) associated with cellulitis in 2005. Blood cultures at the time of the cellulitis were negative and no aetiological factor was identified at the time. On clinical examination in February 2007 he had needle tracks in his right groin, which looked infected clinically. Blood cultures were drawn at admission. Chest radiography revealed that he had multiple pulmonary abscesses in the right lung field. No evidence of airway bleeding or parenchymal bleeding was present. His C-reactive protein (CRP) was 155 mg/L. He was not investigated for pulmonary embolism as he had very poor venous access and a trans-thoracic echocardiogram (TTE) was normal. Investigations for recurrent DVT were negative. The patient absconded on the day of admission, but returned later that day and was started on intravenous flucloxacillin. On day 3, intravenous vancomycin was commenced, as the admission blood culture grew MRSA. He self-discharged on day 4 of hospitalization and was lost to follow-up.

Case B

Case B was a 40-year-old HIV-negative male who was admitted in November 2006. He was a current IDU and had a history of fever, sweating and rapid breathing. On clinical examination he was septic with a right pleural effusion. On day 5 of hospitalization, ultrasound of the chest revealed consolidation of the right lower lobe. He had possible multiple pulmonary abscesses on CT imaging of the chest. TTE and magnetic resonance imaging (MRI) of the spine were normal. One of two blood culture bottles taken on admission yielded MRSA, with Group A streptococcus also being cultured from both bottles. On day 17 of hospitalization he was diagnosed with a right-sided DVT in the central and superficial femoral veins. In addition, blood cultures taken on day 18 grew *Candida* spp. He

was treated initially with ciprofloxacin monotherapy, and subsequently with intravenous vancomycin paired with a single oral agent (clindamycin, followed by rifampicin, followed by ciprofloxacin, in succession, because of side effects), as well as antifungal agents. Vancomycin was stopped as a result of neutropenia and he was changed to oral treatment with rifampicin and ciprofloxacin; he received a total of 28 days anti-staphylococcal treatment. He remained in hospital for a total of 35 days and was discharged on oral rifampicin and ciprofloxacin for a further 14 days, giving a total of 49 days of antibiotic therapy. His compliance with the antibiotic prescription during his outpatient treatment is not known. He was readmitted in January 2007, 5 days after he would have theoretically discontinued his oral antibiotics, with bilateral lower leg abscesses. Blood cultures could not be taken because of access problems. The patient received 1 day of intravenous vancomycin and 5 days of intramuscular teicoplanin, followed by 6 weeks of oral rifampicin and ciprofloxacin. He has not attended hospital appointments since and is lost to follow-up.

Case C

Case C was a 40-year-old male who was admitted in October 2006 with his second episode of MRSA bacteraemia. He was a known IDU, who was HIV-negative, and had a 5-day history of cough with sputum production and left-sided chest pain. He had a past medical history of empyema in 2004 and bilateral ante-cubital abscesses in 2005. In May 2006 he developed cellulitis and abscesses of the left thigh which contained MSSA, necessitating drainage, and bacteraemia with MRSA. These isolates were not submitted for further typing. On examination in October 2006 he had a right femoral aneurysm and chest radiography revealed a right empyema and pneumonia with multiple areas of consolidation. There was no evidence of airway or parenchymal bleeding. His CRP was 238 g/L and blood gas analysis showed a metabolic acidosis. He required continuous positive airway pressure (CPAP) support in the Intensive Therapy Unit (ITU). Blood cultures taken on admission (18.10.06) yielded MRSA. He received 2 weeks of intravenous vancomycin and was subsequently prescribed 2 weeks of doxycycline and rifampicin therapy. Unfortunately he defaulted on treatment. This patient was readmitted in March 2007 with osteomyelitis after malunion of a scaphoid fracture, associated with bacteraemia as a result of MSSA (susceptible to erythromycin and fusidic acid) and readmitted again with recurrent infection in May 2007, at which point he had a *Streptococcus mitis* bacteraemia.

Case D

Case D was a 40-year-old HIV-negative male who was a known IDU. He first presented in October 2006 with a history of back pain and shortness of breath. He had a past medical history of cellulitis in 2001 and was positive for hepatitis C virus. He was diagnosed with discitis with osteomyelitis at T8/T9 on MRI with gadolinium enhancement. Blood cultures from all six bottles taken on admission yielded MRSA, and he received 8 weeks of intravenous vancomycin. This was followed by oral rifampicin and doxycycline. In September 2007, a repeat MRI of the patient's lumbar spine, because of recurrence of lower back pain, did not show any evidence of residual infection.

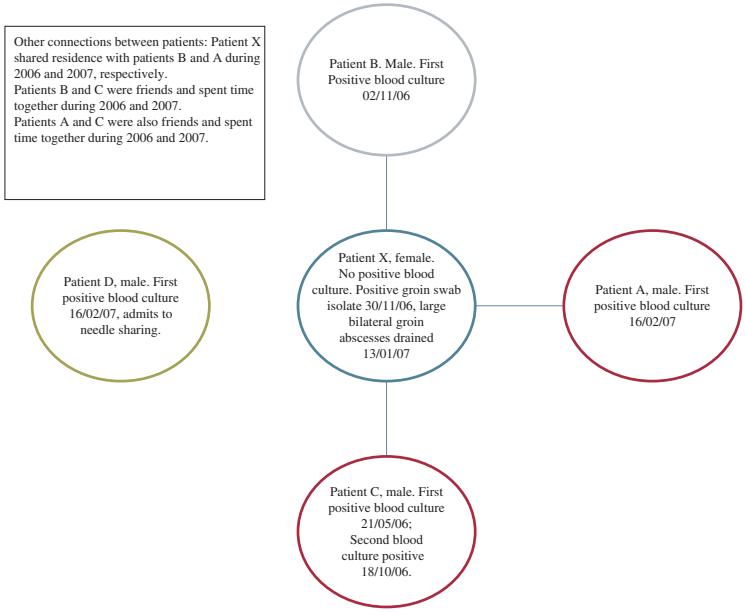

FIG. 1. Known epidemiological links between cases A–D.

Epidemiology

The four individuals lived at different addresses in Cambridgeshire and came into contact with each other over the course of their presentations. Their known associations are presented in Fig. 1. Patients A and C were connected through both being 'friends' with patient B. Patient D had admitted sharing needles on various occasions with other local Cambridge IDUs although no direct connection between him and the other patients was elucidated. A fifth patient (patient X) presented with a clinical picture similar to those of the four cases described. Ciprofloxacin-susceptible MRSA was cultured from a wound swab in October 2006, 2 months before she presented with severe bilateral thigh abscesses. Blood cultures or pus samples were not obtainable. This patient resided at the same address as two of the patients in this series, albeit over separate times. All of these patients, with the exception of patient D, had slept at least overnight in at least one of the few Cambridge hostels.

Phenotypic and molecular investigations

Detailed phenotypic and genotypic characterization of isolates was performed because all four isolates were ciprofloxacin susceptible (an unusual finding for classic HA-MRSA in the UK) (Table 1). In summary, all four were resistant to β-lactams, erythromycin and fusidic acid, and one isolate exhibited additional resistance to gentamicin. All four harboured the *mecA* gene and gave indistinguishable phage patterns (lysed by Group I/III phages). Three isolates were subjected to MLST and were ST1. All four MRSA isolates harboured SCC*mec* type IV (class B *mec* complex and ccrAB2 *ccr* complex) (Table 1). The toxin gene profiles were similar: all were PVL negative but harboured *seh* (enterotoxin gene H); three of four isolates also encoded *sea (*enterotoxin gene A). They were closely related by PFGE according to the criteria of Tenover *et al.* [21] and three isolates were indistinguishable from a control strain of ST1-MRSA-IV from an IDU elsewhere in the UK (Fig. 2). The fourth isolate (Lane 3, patient A) shows a band shift but was closely related to the remainder; this was the gentamicin-resistant isolate.

Discussion

The identification of four ciprofloxacin-susceptible MRSA isolates over a 5-month period from blood cultures of patients known to inject drugs prompted review of the clinical cases together with molecular epidemiologic investigations. The cases of bacteraemia we describe were all associated with involvement of multiple clinical sites, including soft tissues as well as lung tissue (Table 1). None of the pneumonias was clinically necrotizing, as commonly described with CA-MRSA which are PVL-positive, in that there was no clinical or radiographic evidence of haemorrhage. All patients survived the event. As the cases involved IDUs, difficulties in management included (i) establishing intravenous access; (ii) performing blood cultures appropriately without using potentially colonized or infected sites; (iii) completing treatment; and (iv) issues with compliance and follow-up.

A study from South London between 2000 and 2006 identified probable CA-MRSA infection (using ciprofloxacin susceptibility as a marker) in 65 patients with medical record evidence of injecting drug use or alcohol abuse [18]. Of the corresponding isolates, only seven were from blood cultures, averaging one bacteraemia per year. Clearly our cluster of four bacteraemic cases in five months was highly unusual. There have been no cases of bacteraemia with ciprofloxacin-

TABLE 1. Cases of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: details of clinical infections, antibiotic treatment, phenotypic and genotypic characteristics of isolates

Case	Gender, age (years)	Date of blood culture	R-type	Phage type	PVL toxin genes	Other toxin genes	MLST	SCC*mec* type	Likely clinical focus	Antibiotic treatment
A	M, 24	16.02.07	Oxa, Ery, Fus, Gent	A[a]	Neg	*Sea; seh*	ST1	IV	Pulmonary abscesses Cellulitis	Flucloxacillin × 2/7 Vancomycin × 1/12; self-discharged
B	M, 40	2.11.06 mixed with Group A Streptococcus	Oxa, Ery, Fus	A	Neg	*seh*	Not done	IV	Pulmonary abscesses Pneumonia pleural effusion Deep venous thrombosis (DVT) Resolving groin abscess	Ciprofloxacin × 8/7, followed by (Vancomycin, see text + Rifampicin) × 1/12 Clindamycin × 2/52 (in view of Group A Streptococcus)
C	M, 40	21.05.06	Oxa, Ery, Fus	Not done	Neg	*sea; seh*	Not done	Not done	Bacteraemia	Vancomycin
		18.10.06	Oxa, Ery, Fus	A	Neg	*sea; seh*	ST1	IV	Empyema pneumonia Previous cellulitis	Vancomycin × 2/52; self-discharged after this
D	M, 40	13.10.06	Oxa, Ery, Fus	A	Neg	*sea; seh*	ST1	IV	Osteomyelitis Discitis T8/T9	Vancomycin × 2/12, followed by oral Rifampicin and Doxycycline

[a]Isolates gave indistinguishable patterns and were lysed by group I/III phages.
Oxa, oxacillin; Ery, erythromycin; Fus, fusidic acid; Gent, gentamicin.
sea = enterotoxin gene A; *seh* = enterotoxin gene H.

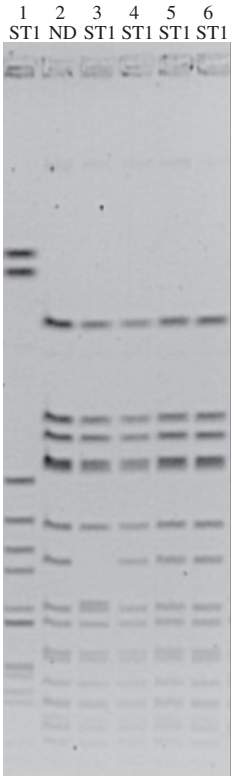

FIG. 2. Macrorestriction of chromosomal DNA, digested with *Sma*I and visualized by pulsed-field gel electrophoresis (PFGE). The sequence types (ST) are also marked (ND, Not Done); Lane 1 = EMRSA-15, variant B1 control strain; Lane 2 = Patient B; Lane 3 = Patient A; Lane 4 = Patient C; Lane 5 = Patient D; Lane 6 = HPA control isolate from known IDU.

susceptible MRSA in IDUs admitted to our hospital between February 2007 and December 2008.

Resistance typing revealed that three isolates were resistant to β-lactams, erythromycin and fusidic acid, and the fourth isolate (from patient A) also exhibited resistance to gentamicin. There was no record of patient A having received gentamicin at our hospital. The association of fusidic acid resistance in MRSA isolates from IDUs in the UK was first highlighted by Corkill *et al.* [19], from the Royal Liverpool University Hospital. They reported an increasing number of fusidic acid-resistant MRSA isolates between 2001 and 2003 (5% in 2001, 7% in 2002 and 12% in the first 8 months of 2003), whereas the rate of fusidic acid resistance in MSSA remained at a constant 13%. Although this Liverpool study involved the general population, the findings concerning the IDU patients had first alerted the authors to this association. The isolates of MRSA causing bacteraemias in IDUs were clonal as shown by PFGE [20].

The ST1-MRSA-IV clone has been reported previously in Australia where it is known as WA-MRSA-1 [22]. It has also been identified in neonatal units in the UK [23–25] and is known to have been circulating among IDUs in England and Wales since approximately 2001 [26]. Between April 2003 and March 2007, 60 isolates of MRSA from IDUs were received by the HPA Staphylococcus Reference Unit for analysis from different areas of England and Wales. Twenty-one of these 60 isolates (35%) were from cases of bacteraemia, 30 were from patients with injection site abscesses or skin infections, four were from patients with endocarditis, and one was from a patient with pneumonia (clinical data are not available for the remaining four) [27].

The ST1-MRSA-IV clone is distinct from healthcare-associated MRSA in the UK (EMRSA-15 and EMRSA-16). Although this community-associated clone does not produce the PVL toxin, it can cause skin and soft tissue infection (SSTI) [28]. In our homeless community in Cambridge, UK, MRSA is a known cause of SSTIs. A retrospective study of SSTIs as a result of MRSA in people who were homeless or at risk of homelessness in 2006–2007 found that 80% (68/85) of MRSA infections occurred in known IDUs [5].

In summary, isolates belonging to the ST1-MRSA-IV lineage were responsible for four cases of bacteraemia in IDUs in Cambridge. These cases were complicated in terms of presentation, involvement of several clinical sites, and the complex management issues surrounding this population group. There were known epidemiological links among three individuals, and molecular typing showed that all four carried isolates of the the ST1-MRSA-IV lineage which is known to be circulating among IDUs in England and Wales. To improve our understanding of the epidemiology and burden of disease associated with this lineage, other centres need to remain vigilant to ensure that cases do not go unrecognized.

Author Contributions

F.J.C. and N.M.B. advised on initial diagnosis and management of the patients and wrote the initial draft of the manuscript, E.G.-K. and A.C. had clinical responsibility for the patients during their hospital stay and summarized the epidemiological relationships, J.C.H. performed the literature review, M.S., M.G. and A.K. performed the molecular work. All authors commented on subsequent versions of the manuscript.

Transparency Declaration

No financial support was sought and no conflicts of interest are declared.

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