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# *Staphylococcus aureus* bacteraemia associated with injected new psychoactive substances

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## SUMMARY

Injecting drug use is often associated with deep-seated infection. In Lothian in Scotland there has been a recent increase in the use of injected new psychoactive substances (NPS). Patients who have injected NPS have presented with *Staphylococcus aureus* bacteraemia (SAB) with life-threatening complications. We describe a unique case-series of 14 episodes of SAB in ten patients. Users of injected NPS had a significantly higher incidence of endocarditis and cavitating pulmonary lesions ($P < 0{\cdot}05$) compared to those who inject only opiates. Cases of SAB in people who inject NPS have contributed to a significant rise in the overall incidence of SAB in people who inject drugs ($P < 0{\cdot}05$) which has in turn impacted on the ability of Lothian to meet national targets for reducing the incidence of SAB.

**Key words**: Bloodstream infections, endocarditis, injecting drug use, pulmonary abscess *Staphylococcus aureus*.

## INTRODUCTION

In recent years there has been a rapid increase in the use of new psychoactive substances (NPS) by people who inject drugs (PWID) in Scotland [1]. These include several different classes of active ingredient, including synthetic cannabinoids and synthetic cathinones [2]. Although some of these substances have been made illegal in certain jurisdictions, there remains a wide variety of subtly altered variants that have not yet been legislated against and have indeed been manufactured deliberately to circumvent existing laws [3]. Prior to 2009, NPS were not reported as a factor, causative or not, in any deaths related to drugs in Scotland. Since then there has been an increasing number seen, with 113 deaths in 2013 mentioning NPS as a factor [1].

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NPS can be purchased in Scotland through many routes, including directly from dealers, internet marketing and retail outlets ('head shops'). They have been adopted by many PWID as alternatives to more traditional drugs of misuse such as opiates owing to their availability, legality, relatively low cost and perceived safety [2, 4, 5].

Among PWID, some NPS are referred to as 'bath salts' due to their visual similarity to bathing salts [2, 4]. One such substance known as 'Burst' is a NPS that was popular in the Lothian area of South East Scotland during the study period [Scottish Drugs Forum (SDF), personal communication], a population of about 830 000 served by NHS Lothian [6]. Although 'bath salts' typically contain synthetic cathinones, related to an amphetamine analogue derived from the plant *Catha edulis* (khat) [2, 4, 7], the ingredients found in 'Burst' tend to be more variable. During the period of this study, methiopropamine (MPA), butylone and ethylphenidate were known to be in local circulation in 'Burst' (SDF,

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personal communication). None of these substances was subject to control under the Misuse of Drugs Act [8] during the study period. Usually the active ingredients will be mixed with one or more adulterants including caffeine, lidocaine and piperazines. Even in identically packaged samples there can be significant variation in the contents with regard to the proportion of active ingredients and batches are not standardized [7, 9].

Synthetic cathinones activate central and peripheral monoamine systems, particularly affecting transport of serotonin, dopamine and norepinephrine, with effects similar to amphetamines or cocaine [2, 3, 10]. They have been shown in an animal model to act as potent reinforcers with high addictive potential [3]. Repeated dosing in quick succession is often seen in users of 'bath salts', which can be ingested, snorted, smoked, injected or used rectally [4, 8]. An important feature of 'Burst' seems to be the rapidity of onset of euphoria once injected, sometimes with the needle left *in situ*, leading to increased soft tissue damage (SDF, personal communication).

Despite the perceived safety of 'bath salts' within the drug-using community locally, there is increasing concern about associated adverse effects within the medical community [2, 4, 11]. Acute psychosis with agitation, hallucinations, high-risk behaviour that facilitates transmission of blood-borne viruses and aggression are frequent causes of presentation to emergency departments and psychiatric services [2, 3, 5]. Physiological effects include tachycardia, hypertension and hyperthermia [11]. Electrolyte disturbances and disseminated intravascular coagulation may be seen, as may renal impairment, seizures and myocardial infarction [2, 12]. Serotonin syndrome can develop, in some cases progressing to potentially fatal rhabdomyolysis [8, 13]. Hepatic toxicity and nerve-end toxicity have been reported from animal models [9, 14]. There have been fatalities, associated particularly with synthetic cathinone use and these have shown similar pathological findings to deaths attributed to amphetamines [9].

There are few publications describing the incidence or range of infections associated with injecting 'bath salts'. A recent case series from Dublin described severe soft tissue infections with cellulitis, thrombophlebitis and extensive abscess formation in four users of mephedrone, requiring surgical intervention in three [15]. Extravasation of 'bath salts' seemed to be particularly damaging, with local necrosis observed. A case report in 2012 described severe cellulitis and necrotizing fasciitis [16].

A case-series from New York described three injectors of 'bath salts' who presented with disseminated *Staphylococcus aureus* infection. Two of these had confirmed tricuspid valve endocarditis, while a third displayed electrocardiogram changes consistent with pericarditis. All three had cavitating lung lesions while one had septic polyarthritis [11].

There are several reasons why people who inject 'bath salts' may be more prone to invasive bacterial infection. Unlike opiates, 'bath salts' are purchased as crystals or powders which are then easily dissolved in water without heating. The absence of heating may allow survival of any bacteria contaminating the product in the injected solution. The solution itself may still contain particulate matter resulting in increased vascular damage and local necrosis. Extravasated solution is corrosive to soft tissue which may facilitate entry of endogenous skin organisms such as *S. aureus* through the normal skin barrier to cause deeper local infection or bacteraemia. In addition to the damage caused by the injected solution, there is also often evidence of multiple puncture sites at the same location further damaging the integrity of the skin [5, 11, 15, 16] (SDF, personal communication).

*S. aureus* bacteraemia (SAB) is a condition associated with high morbidity and mortality which can be as great as 30% [17]. The incidence varies from 19·7/100 000 to 50·0/100 000 population and is typically higher in older individuals, those from less prosperous socioeconomic groups and those with co-morbid medical conditions [18]. Risk factors for mortality include older age, underlying malignancy, low body mass index, anaemia and low albumin, while those patients with complex disease such as endocarditis or pulmonary infection are also more likely to die [18–21]. Invasive *S. aureus* infection can present with deep-seated metastatic lesions, severe skin and soft tissue infection, septic deep vein thrombosis, bone and joint infection (BJI), necrotizing pneumonia, septic arthritis and infective endocarditis [17, 22].

Healthcare Improvement Scotland (HIS) advocates that all cases of SAB should be managed directly by or with input from an infection specialist and all patients should undergo echocardiography, ideally with input from a cardiologist [17, 23, 24]. Management involves prompt identification and removal of infective foci, in conjunction with appropriate intravenous antibiotic therapy. While no clear consensus exists regarding optimal antibiotic agents and duration of therapy, expert opinion advocates a minimum of 14 days intravenous therapy for 'uncomplicated' bacteraemia, and longer

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(4–6 weeks) where the focus cannot be removed or where the patient remains bacteraemic [18, 25, 26]. Undertreating SAB results in higher incidence of relapse of bacteraemia [17, 24].

Since 2013, infection specialists in Lothian have observed an increasing incidence of complicated SAB in PWID. Many have an association with the injection of 'bath salts', particularly the brand known as 'Burst'. Here we report a case-series of complicated *S. aureus* disease associated with the use of NPS in Edinburgh.

## METHODS

A retrospective case-series of PWID with SAB was identified as part of an audit of SAB management in Lothian. Our electronic laboratory information management system (APEX, IBM, USA) was interrogated to identify all cases of SAB seen in Lothian from 1 October 2012 to 30 September 2014. To avoid counting the same episode of SAB more than once repeat isolates from within 14 days of an initial positive blood culture were considered to be from the same bacteraemic episode. From this initial patient group, the electronic patient record (TrakCare, Intersystems, UK) was consulted in order to identify if patients had died within 90 days of the date the last positive blood culture growing *S. aureus* had been taken.

APEX and TrakCare records for those individuals aged between 12 and 60 years at the onset of SAB, were investigated further for information regarding intravenous drug use. Patients outside this age group were excluded as injecting drug use is not common in these extremes of age. The same records were reviewed for documentation of injecting drug use in association with the onset of SAB (up to 30 days beforehand) and the type of drug injected, where named, was recorded. These records were also examined for 5 years prior to the diagnosis of SAB for any evidence of past use of injected NPS. Patients who injected drugs were divided into two groups; those who were known injectors of NPS, whether exclusively or in combination with other substances: and those who had no record of injecting NPS.

Where evidence of injecting drug use was found, electronic clinical records were further examined for evidence of severe complications of SAB. Any surgical intervention such as debridement or incision and drainage that was carried out was noted. The duration of hospital stay was obtained, and whether there was recurrence of bacteraemia. The duration and choice of intravenous antibiotic therapy, was also recorded.

Two similar time periods (October 2012–September 2013 and October 2013–September 2014) were identified to compare any change in incidence of SAB associated with NPS injecting, and any other change in incidence of other *S. aureus* infective manifestations. Additionally, length of hospital stay and duration of antibiotic therapy were compared. Information regarding numbers of acute occupied bed days over this time was taken from Health Protection Scotland (HPS) data [27].

Isolates of *S. aureus* from patients with documented use of injected NPS were sent to the Scottish MRSA Reference Laboratory (SMRSARL, Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde) to fulfil criteria for mandatory SAB reporting in Scotland [28]. The isolates were typed by *spa* gene polymorphisms [29] to determine epidemiological linkage or their genetic diversity. Isolates were also tested by PCR for the presence of the Panton–Valentine leukocidin (PVL) toxin gene [30].

### Ethical approval

Advice was sought from the South East Scotland Research Ethics Service regarding access to patient information. As this study was based on data obtained in the course of normal patient care, with no communication of identifiable patient data, no formal ethical review was required.

### Statistical analysis

Statistical analysis was performed using Instat (GraphPad Software, USA). Parametric variables were compared using Fisher's exact test. Non-parametric variables were compared using the Mann–Whitney test with two-tailed $P$ values, as the distribution of data in these sets was found to be non-normal using modified Kolmogorov–Smirnov testing. Non-parametric variables were further compared using unpaired $t$ testing with Welch correction, in case any datasets were in fact normally distributed: this did not change the significance of any outcome and the results have therefore not been detailed.

## RESULTS

A comparison of the overall incidence of SAB in PWID in the two time periods (October 2012–September 2013 and October 2013–September 2014)

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Table 1. *Changing trends in all cases of SAB in Lothian between 2012–2013 and 2013–2014*

| | October 2012 to September 2013 | October 2013 to September 2014 | *P* value |
|---|---|---|---|
| Total cases of SAB in Lothian | *N* = 251 | *N* = 253 | |
| Incidence per 100 000 population | 30·24 | 30·48 | |
| Acute occupied bed days | 805 052 | 822 082 | |
| Rate of SAB per 1000 acute occupied bed days | 0·32 | 0·31 | |
| 30-day mortality | 40 (15·94%) | 42 (16·60%) | |
| SAB associated with injecting drug use (%) | 10 (3·98%) | 26 (10·28%) | 0·0087 |
| SAB associated with injecting NPS (%) | 0 (0%) | 14 (5·53%) | 0·0001 |
| SAB cases in 12–60 years age group (% of total) | *N* = 102 (40·64%) | *N* = 106 (41·90%) | 0·7867 |
| SAB in 12–60 years age group associated with injecting drug use (%) | 10/102 (9·80%) | 26/106 (24·53%) | 0·0058 |
| SAB in 12–60 years age group associated with injecting NPS (%) | 0/102 (0%) | 14/106 (13·21%) | <0·0001 |

NPS, New psychoactive substances; SAB, *Staphylococcus aureus* bacteraemia.

is shown in Table 1. In the latter period there was a significant increase in the proportion of overall cases associated with injecting drug use (3·98–10·28%, $P = 0{\cdot}0087$). This was seen despite no overall increase in incidence of SAB in the 12–60 years age group, the group thought to be likely to encompass all PWIDs (40·64% *vs.* 41·90%, $P = 0{\cdot}7867$). Despite the overall incidence of SAB remaining unchanged between the study periods (251 *vs.* 253) the number of cases associated with injecting drug use increased markedly over this period from 10 to 26. This correlates with an increase in cases associated with injection of NPS from 0 to 14.

Fourteen episodes of SAB in ten individual PWIDs who injected NPS were identified and details of clinical presentation, complications, management and outcomes are shown in Table 2. Subjects had a median age of 34 (range 29–43) years and three were women. Seven were positive for hepatitis C antibody, indicating either current or past infection, and five of these were positive for hepatitis C antigen, indicating current infection.

In nine of the 14 episodes, patients were febrile at presentation (>37·5 °C), and in five episodes a systolic blood pressure of ⩽100 mmHg was recorded. Five displayed tachycardia (>100 bpm). C-reactive protein (CRP) was elevated in all episodes with ten showing values >100 mg/l (normal range 0–5 mg/l); the peripheral white blood cell count was less markedly elevated in most episodes, but counts of $>15 \times 10^9$/l were found in two episodes.

The majority of patients either presented with, or later developed, some form of deep-seated infection as a consequence of SAB. This included four cases of endocarditis, six with cavitating lung lesions and three with septic arthritis, often in combination. Over half of the episodes resulted in incomplete treatment due to patient abscondment or patient could not be contacted for recall after the initial consultation.

All 10 SAB subjects yielded isolates susceptible to methicillin and therefore susceptible to flucloxacillin. No *spa* type was identified from more than one patient. Of the three individuals who presented more than once, two had recurrence of bloodstream infection with the same *spa* type, while the third had isolates of different *spa* types. All isolates were negative for the PVL toxin gene.

Regarding the incidence of serious complications of SAB in the patients from the two study periods (10 and 26, respectively) an increase from 0 to 4, was noted in the absolute numbers of cases of endocarditis and cavitating pulmonary lesions in the latter time period but this did not reach statistical significance. Similarly, there was no significant difference between the length of stay in hospital or the duration of intravenous antibiotic therapy for patients from both study periods.

With reference to clinical outcomes between two groups of PWID, the group using NPS included more patients with endocarditis (4/14 *vs.* 0/22, $P = 0{\cdot}0335$) and those with cavitating pulmonary lesions (6/14 *vs.* 2/22, $P = 0{\cdot}0361$). The rate of recurrence was greater in the group using NPS (3/11 *vs.* 0/20, $P = 0{\cdot}0367$). Other severe complications (BJI and other deep-seated infections) were not seen significantly more often in either group. Both groups had broadly similar median durations of antibiotic therapy but those injecting NPS included a lower proportion that completed at

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Table 2. *Case summaries of SAB associated with injecting NPS in Lothian*

| Case no. | Presentation | At presentation | | | | | Complications of SAB | Antibiotic therapy | | Progress and outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *T* (°C) | BP | HR | WCC | CRP | | Agent | Duration (days) | |
| 1 | Septic arthritis<br>Diarrhoea<br>Shock | 39·2 | 92/54 | 92 | 11·7 | 143 | Cavitating lung lesions<br>Septic arthritis | Flucloxacillin i.v.<br>Rifampicin p.o.<br>Doxycycline p.o. | 28<br>42<br>14 | Completed 28 days i.v. therapy and 14 days p.o. follow-on. Did not attend follow-up and resumed injecting. |
| 2 | Fever<br>Groin pain | 40·1 | 100/52 | 74 | 12·3 | 208 | Femoral vein septic DVT | Clindamycin i.v. | 3 | Absconded prior to diagnosis of SAB. Returned briefly but absconded again prior to treatment. |
| 3 | Pleuritic pain<br>Haemoptysis | 38·4 | 104/70 | 85 | 25·8 | 248 | Endocarditis (TV and MV)<br>Cavitating lung lesions<br>Infective polyarthritis | Meropenem i.v.<br>Vancomycin i.v.<br>Flucloxacillin i.v. | 2<br>2<br>At least 42 | Initial broad-spectrum antibiotics due to sepsis. Rationalized to flucloxacillin. Transferred outside Lothian and completed 42 days i.v. flucloxacillin. |
| 4 | Cellulitis<br>Chest pain | 40·0 | 123/67 | 106 | 9·0 | 42 | None known | Flucloxacillin i.v.<br>Flucloxacillin p.o. | 3<br>14 | Poor compliance with i.v. therapy. Switched to p.o. when discharged against medical advice. |
| 5 | Leg swelling and erythema | 38·5 | 105/44 | 62 | 15·3 | 261 | Femoral vein septic DVT<br>Groin abscess<br>Infected CVC | Flucloxacillin i.v. | 28 | Continued NPS use during admission. Completed planned treatment. |
| 6 | Infected groin injection site | 39·3 | – | 108 | 14·8 | 56 | Groin abscess | Flucloxacillin i.v. | 5 | Absconded during treatment. |
| 7 | Fever<br>Buttock pain<br>Hand pain | 38·6 | 110/77 | 98 | 12·1 | 237 | Paraspinal abscess | Vancomycin i.v.<br>Ceftriaxone i.m. | 7<br>5<br>Unknown | Abscondment and ongoing injecting drug use. Poor compliance with therapy. Never reached therapeutic vancomycin level. Discharged against advice. |
| 8 | Pleuritic chest pain | 37·2 | 89/50 | 70 | 10·7 | 296 | Endocarditis<br>Cavitating lung lesions<br>Empyema | Flucloxacillin i.v.<br>Rifampicin p.o.<br>Clindamycin p.o. | 42 (total) | Flucloxacillin given for 42 days. Absconded with chest drains *in situ* after completing therapy for SAB. |
| 9 | Cellulitis<br>Dyspnoea | 37·0 | 91/60 | 88 | 13·1 | 317 | Endocarditis<br>Cavitating lung lesions<br>Thigh abscess | Flucloxacillin i.v.<br>Clindamycin i.v.<br>Daptomycin i.v. | 79 (total) | Variable clinical course with multiple changes of antibiotic therapy. Completed planned treatment and was well at the time of discharge. Resumed injecting. |
| 10 | Fever<br>Leg swelling | 37·0 | 129/62 | 90 | 9·1 | 57 | None known | Cotrimoxazole i.v. and p.o. | 7<br>Unknown | Absconded after 7 days. Discharged with p.o. therapy on return. Ongoing injecting. |

Table 2 (*cont.*)

| Case no. | Presentation | At presentation | | | | | Complications of SAB | Antibiotic therapy | | Progress and outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *T* (°C) | BP | HR | WCC | CRP | | Agent | Duration (days) | |
| 11 | Out-of-hospital cardiac arrest | 36·3 | 120/80 | 120 | 7·6 | 253 | Endocarditis<br>Cavitating lung lesions | Flucloxacillin i.v.<br>Daptomycin i.v.<br>Cotrimoxazole i.v.<br>Ceftriaxone i.v. | 7<br>6<br>7<br>25 | Did not complete 42 days treatment due to abscondment and injecting drug use via venous access. |
| 12 | Fever<br>Leg and groin pain | 39·8 | 72/43 | 104 | 13·0 | 250 | Groin abscess<br>Cavitating lung lesions | Coamoxiclav i.v.<br>Flucloxacillin i.v. | 3<br>28 | Discharged at end of planned treatment course. |
| 13 | Cellulitis | 36·6 | 122/84 | 77 | 5·1 | 36 | None known | Flucloxacillin i.v. | 1 | Discharged before SAB diagnosed. |
| 14 | Fever<br>Wrist swelling | 38·8 | 109/62 | 114 | 11·6 | 265 | Septic arthritis | Vancomycin i.v.<br>Ciprofloxacin p.o. | 7<br>7 | Underwent washout of septic wrist. Absconded prior to completion of therapy. |

BP, Blood pressure (mm/Hg); CRP, C-reactive protein (mg/l, normal range 0–5 mg/l); CVC, central venous catheter DVT, deep vein thrombosis; HR, heart rate (beats per minute); i.m., intramuscular; i.v., intravenous; MV, mitral valve; NPS, new psychoactive substances; p.o., oral; SAB, *Staphylococcus aureus* bacteraemia; *T*, temperature (degrees Centigrade); TV, tricuspid valve; WCC, peripheral blood white cell count ($\times 10^9$/l, normal range 4–11 $\times 10^9$/l).

least 14 days of intravenous antibiotics than non-NPS injectors (7/14 *vs.* 15/19) but this did not achieve statistical significance.

The impact on NHS Lothian caused by treating these patients was examined. The number of occupied bed days for SAB related to injecting drug use was similar in the two study periods (541 *vs.* 556). However the proportion of these for SAB related to injecting use of NPS increased from 0/541 (0%) to 334/556 (60·07%). Data were not available regarding duration of antibiotic therapy for all patients in the 2012–2013 period so direct comparison is not possible, but in the 2013–2014 period the treatment of SAB associated with injecting use of NPS accounted for 306/492 (62·20%) of the total number of days of intravenous antibiotic therapy given for SAB associated with injecting drug use over this time.

## DISCUSSION

Lothian in South East Scotland has seen a recent increase in the use of injected NPS, in many cases replacing the more established drugs of misuse such as heroin. These agents are many and varied, with regards to the psychoactive substances that they can contain and demonstrate significant batch to batch variation even for products sold with the same name. While NPS are often perceived by PWID to be safer, we report a disturbing correlation with complicated SAB in 14 episodes in ten patients.

Their illnesses came to our attention because they represented a noticeable and sudden increase in the incidence of complicated SAB being detected and investigated as part of the national SAB surveillance programme in Scotland. Such infections are potentially life threatening – we report four cases of *S. aureus* endocarditis. None of these patients underwent valve replacement surgery but six of the 10 patients had cavitating pulmonary lesions, with some cases progressing to rupture and development of pneumothorax and/or empyema. Groin infections, septic thrombi and BJIs were also seen with very few presenting with an identifiable primary focus. It is not currently known whether the causative isolates of *S. aureus* exhibited increased pathogenicity or how much was due to an associated change in host injecting behaviour.

The agents being injected are corrosive to tissue if extravasation from veins into surrounding tissues occurs resulting in more substantial soft tissue damage often in an anatomical relationship to areas where

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*S. aureus* carriage is common such as the groin thus facilitating entry into the bloodstream. From discussion with the affected PWID, larger bore needles may be required for the injection of NPS and the frequency of the skin puncture is much higher when using NPS as the onset of exhilaration is more rapid and duration shorter compared to opiates; this results in a desire to maintain the effect through repeat injection. Additionally the rapidity of onset of exhilaration can result in the needle remaining *in situ* for longer while euphoric resulting in more tissue and vascular damage than with heroin. The solution injected may not be filtered and thus contain particulate matter which may account for a higher incidence of abscesses in areas such as lung where particulates may not be able to pass through capillaries. Moreover, the solution, unlike heroin, may not be heated which facilitates survival of *S. aureus* in the injected solution. Additionally, 'cleaning' of injecting equipment with saliva may introduce contamination from oral flora [31, 32]. Consequently, the route of entry of *S. aureus* into the bloodstream is unclear but factors specific to NPS injection may be contributory.

The finding that more than half of the study patients either had active hepatitis C infection at the time of presentation or were antibody positive without evidence of active disease, is suggestive of a history of chronic injecting drug use and high-risk injecting possibly through shared equipment. None of them had previously been diagnosed with SAB so relapse of previous infection did not appear to be a factor at their first presentation.

As the *spa* type of the *S. aureus* isolates indicated high genetic diversity, a point-source outbreak due to contamination of the injected substances prior to packaging, or person-to-person transmission between PWID was therefore unlikely but suggests rather that the individuals were involved in a behaviour that facilitated *S. aureus* infection due to their own endogenous flora. Interestingly, two *spa* types, t015 and t189, feature among the 20 most common *spa* types isolated in Europe in the last 5 years but the other types are not commonly encountered [33]. The absence of PVL genes in these strains is notable despite the presence of severe complications in many of these patients, including abscesses and cavitating lung lesions.

Our findings indicate that underlying infective endocarditis or cavitating lung lesions, but not other deep-seated infections, were statistically associated with NPS injection rather than with injection of other drugs. Additionally, injectors of NPS appeared to have a higher rate of SAB recurrence than with other drugs which further adds to the *S. aureus*-associated morbidity with NPS injection and the impact on inpatient services for optimal treatment.

Despite the increased number of cases with complex manifestations their median hospital stay was shorter. This was due in part to a significant rate of absconding of these patients; 9/14 treatment episodes ended prematurely as the patient failed to comply or had left the hospital; in some cases there was no opportunity for an infection specialist to review the patient. The healthcare experience of this vulnerable group may require further evaluation as the inpatient environment may not necessarily provide the best chance of achieving appropriate treatment. It may therefore be worthwhile exploring engagement with community treatment facilities or drug specialist nurses to administer intravenous antibiotics daily via temporary infusion devices.

At presentation there was no clear association between blood pressure or temperature and the incidence of severe complications. However, in patients with deep-seated complications not directly related to the injection site such as endocarditis, cavitating pulmonary lesions, paraspinal abscess or septic arthritis (i.e. excluding groin abscess or septic deep vein thrombosis), the median CRP was significantly raised compared to patients without these features (251·5 mg/l *vs.* 56·5 mg/l). The most commonly prescribed antibiotic was flucloxacillin, either as monotherapy or in combination with other agents. Vancomycin was preferred in the presence of allergy to penicillin or as part of combination therapy in the presence of endocarditis with severe sepsis.

None of the patients in this series died despite SAB generally being considered to have an associated mortality of around 30% [17]. Overall, the 90-day mortality rate for all SAB cases in Lothian was 22·71% in the year to September 2013 and 23·47% in the year to September 2014. Mortality at 90 days was chosen over 30 days as some patients were being managed for endocarditis, a condition typically requiring longer duration of treatment. The high survival rate is difficult to explain but several patients presented with severe illness and consequently there was often little delay in starting appropriate antimicrobial therapy, especially when a history of injecting drug use was known from the outset. However, despite prompt initial antimicrobial and sepsis management, 14/36 (38·9%) of SAB patients associated with injecting

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drug use did not complete the recommended minimum of 14 days intravenous antimicrobial therapy [22]. It may be an important factor that the cohort of PWID (median age 35·5, range 26–58 years) are generally younger and have greater physiological reserve than the non-PWID cohort (median age 65·5, range 0–98 years) who had higher SAB-associated mortality.

The overall incidence of SAB in Lothian did not change between the two periods studied, or in the age group (12–60 years) which was more likely to include the majority of PWID. Nevertheless, the proportion of SAB associated with injecting drug use more than doubled, from 3·98% to 10·28% of the affected population ($P = 0{\cdot}0087$) and from 9·80% to 24·53% in the 12–60 years age group ($P = 0{\cdot}0058$). This increase is accounted for by SAB cases where the use of injected NPS was documented. The total number of bed occupancy days for SAB associated with injecting drug use did not change (541 *vs.* 556 days) but the number of days of intravenous antibiotics administered appears to have risen sharply, allowing for the fact that data are missing in the first period studied for 3/10 patients. This is possibly due to a more recent requirement for prolonged antimicrobial treatment but more likely reflected a higher proportion completing the required 14 days of intravenous treatment; the increasing impact on acute hospital services was clear.

Scottish Government performance targets (HEAT targets) for Healthcare Associated Infection (HAI) currently require all NHS areas in Scotland to reduce their rates of SAB to $\leqslant 0{\cdot}24$/1000 acute occupied bed days by March 2015 [28]. Within NHS Lothian all SAB cases are required to be reviewed by an infection specialist doctor and a root cause analysis investigation of each SAB case by an infection control nurse. The former is facilitated by twice-weekly infection consult rounds at all three major acute hospitals within NHS Lothian.

The proportion of SAB cases acquired in the community through injecting drug use (10% of all SAB in Lothian in 2013/2014) with a rising incidence due to NPS injection in the community unrelated to healthcare attendance, demonstrates that SAB incidence is not as representative of HAI standards as it is often perceived to be and cannot definitely be assumed to indicate poor HAI standards within healthcare facilities. Overall the SAB incidence in the two time periods (Table 1) appears unchanged but this masks a rise in SAB cases in PWID and a fall in the incidence of SAB from other causes, suggesting that HAI-related SAB is actually falling as a consequence of quality improvement measures but being replaced by SAB due to injecting drug use. Data gathered to support Scottish Government targets to reduce the infection rate of SAB show an overall reduction in the period 2008–2013 but this trend has not continued into 2014, with Lothian's infection rate of 0·31/1000 occupied bed days reflecting the national average.

Being able to identify that SAB cases are associated with injecting drug use and NPS use in particular relies on good record keeping on behalf of clinicians. It also relies on the patient admitting to use of particular substances which they may be reluctant to do for a variety of reasons. It may be that NPS injecting was underreported by users prior to 2014 but multidisciplinary feedback from agencies working locally with PWID suggests that this is genuinely a new phenomenon. It is also possible that lack of awareness of the myriad of new substances that fall into the category of NPS among medical staff meant that these substances were not documented or their significance not appreciated. As such there is a need to continue to raise awareness of these new trends in injecting behaviour and the marked change in infective illnesses that appear to be associated with them.

Some limitations of this study are evident. Cases were identified through patients admitting that they have injected NPS and as such we may not have accurately identified the true scale of this problem and our findings could likely be an underestimation. Moreover, following the period of data collection there was a sharp increase in the number of cases diagnosed of endocarditis associated with NPS injection, and this requires further studies in collaboration with cardiologists. Other clinical problems associated with injection of NPS include cases of *Streptococcus pyogenes* infection and increased diagnoses of hepatitis C infection. These were outside the scope of the present study.

In conclusion, we describe a disturbing association manifesting in the Lothian region of South East Scotland where there has been an appreciable and significant increase in the incidence of SAB often with severe clinical complications. This coincides with a change in behaviour among PWID locally whereby injection of NPS (particularly ethylphenidate and methiopropamine) has become much more common. These agents are perceived by users to be a safer alternative to opiates but the rapid rise in

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incidence of complex *S. aureus* infection does not support this view. Given the rapid increase in availability, legality of use and more favourable cost compared to opiates for NPS this is a deeply concerning development and may represent the initial manifestations of what may become a much bigger and more widespread problem if this behaviour continues or is adopted elsewhere. This rising incidence of SAB in turn impacts significantly on local acute hospitals as well as primary care and demonstrates a limitation of using SAB incidence as a surrogate marker of HAI.

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## DECLARATION OF INTEREST

None.

## REFERENCES

1. **Scottish Government: Drug-related deaths in Scotland in 2013.** (http://www.nrscotland.gov.uk/files//statistics/drug-related-deaths/2013/drugs-related-deaths-2013.pdf). Accessed 9 June 2015.
2. **Aoun EG, Christopher PP, Ingraham JW.** Emerging drugs of abuse: clinical and legal considerations. *Rhode Island Medical Journal* 2014; **97**: 41–45.
3. **Baumann MH, *et al.*** Bath salts, spice and related designer drugs: the science behind the headlines. *Journal of Neuroscience* 2014; **34**: 15150–15168.
4. **Johnson PS, Johnson MW.** Investigation of 'bath salts' use patterns within an online sample of users in the United States. *Journal of Psychoactive Drugs* 2014; **46**: 369–378.
5. **Scottish Drugs Forum: NPS in Scotland – Health Impacts.** (http://www.sdf.org.uk/resources/reports-and-research/#3). Accessed 9 June 2015.
6. **Scotland's Census 2011.** (http://www.scotlandscensus.gov.uk/). Accessed 9 June 2015.
7. **Schneir A, *et al.*** Comprehensive analysis of 'bath salts' purchased from California stores and the internet. *Clinical Toxicology* (*Philadelphia*) 2014; **52**: 651–658.
8. **Scottish Drugs Forum Information Sheet.** MPA (Methiopropamine) (www.sdf.org.uk/index.php/download_file/view/670/106/). Accessed 9 June 2015.
9. **Araujo AM, *et al.*** Raising awareness of new psychoactive substances: chemical analysis and in vitro toxicity screening of 'legal high' packages containing synthetic cathinones. *Archives of Toxicology* 2015; **89**: 757–711.
10. **Iversen L, *et al.*** Neurochemical profiles of some novel psychoactive substances. *European Journal of Pharmacology* 2013; **700**: 147–51.
11. **Belton P, *et al.*** Cardiac infection and sepsis in 3 intravenous bath salts drug users. *Clinical Infectious Diseases* 2013; **56**: e102-e104.
12. **Banks ML, *et al.*** Synthetic cathinones ('bath salts'). *Journal of Emergency Medicine* 2014; **46**: 632–642.
13. **Hohmann N, Mikus G, Czock D.** Effects and risks associated with novel psychoactive substances: mislabelling and sale as bath salts, spice and research chemicals. *Deutsches Arzteblatt International* 2014; **111**: 139–147.
14. **Martinez-Clemente J, *et al.*** Dose and time-dependent selective neurotoxicity induced by mephedrone in mice. *PLoS ONE* 2014; **9**: e99002.
15. **Dorairaj JJ, *et al.*** The untold truth about 'bath salt' highs: a case series demonstrating local tissue injury. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 2012; **65**: e37-e41.
16. **Russo R, *et al.*** Life-threatening necrotizing fasciitis due to 'bath salts' injection. *Orthopedics* 2012; **35**: e124–127.
17. **Thwaites GE, *et al.*** Clinical management of *Staphylococcus aureus* bacteraemia. *Lancet Infectious Diseases* 2011; **11**: 208–222.
18. **van Hal SJ, *et al.*** Predictors of mortality in *Staphylococcus aureus* bacteraemia. *Clinical Microbiology Reviews* 2012; **25**: 362–386.
19. **Kobayashi D, *et al.*** A predictive rule for mortality of inpatients with *Staphylococcus aureus* bacteraemia: a classification and regression tree analysis. *European Journal of Internal Medicine* 2014, **25**: 914–918.
20. **Fortuin-de Smidt MC, *et al.*** *Staphylococcus aureus* bacteraemia in Gauteng academic hospitals, South Africa. *International Journal of Infectious Diseases* 2014; **30**:41–48.
21. **Jensen AG, *et al.*** Treatment and outcome of *Staphylococcus aureus* bacteraemia: a prospective study of 278 cases. *Archives of Internal Medicine* 2002; **162**: 25–32.
22. **Ye R, *et al.*** Clinical characteristics of septic pulmonary embolism in adults. *Respiratory Medicine* 2014; **108**: 1–8.
23. **Healthcare Improvement Scotland.** Guidance on management of proven or suspected *Staphylococcus aureus* bacteraemia in adults (January 2013) (https://www.scottishmedicines.org.uk/files/sapg1/SAB_algorithm__grey-scale_.pdf). Accessed 9 June 2015.
24. **Holland TL, Arnold C, Fowler Jr. VG.** Clinical management of *Staphylococcus aureus* bacteraemia: a review.

https://doi.org/10.1017/S095026881500271X Published online by Cambridge University Press

*Journal of the American Medical Association* 2014; **312**: 1330–1341.

25. **Lopez-Cortes LE, *et al.*** Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of *Staphylococcus aureus* infection. *Clinical Infectious Diseases* 2013; **57**: 1225–1233.
26. **Gould FK, *et al.*** Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom. *Journal of Antimicrobial Chemotherapy* 2009; **63**: 849–861.
27. **Health Protection Scotland.** Weekly report (13 January 2015) including commentary on quarterly epidemiological data on *Staphylococcus aureus (S. aureus)* bacteraemia infection in Scotland, July to September (Q3) 2014 (http://www.hps.scot.nhs.uk/documents/ewr/pdf2015/1502.pdf). Accessed 9 June 2015.
28. **Scottish Government HEAT targets for NHS Scotland.** (http://www.scotland.gov.uk/About/Performance/scotPerforms/partnerstories/NHSScotlandperformance/SAB). Accessed 9 June 2015.
29. **Harmsen D, *et al.*** Typing of methicillin-resistant *Staphylococcus aureus* in a university hospital setting by using novel software for *spa* repeat determination and database management. *Journal of Clinical Microbiology* 2003; **41**: 5442–5448.
30. **Lina G, *et al.*** Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clinical Infectious Diseases* 1999; **29**: 1128–1132.
31. **Brett MM, *et al.*** Soft tissue infections caused by spore-forming bacteria in injecting drug users in the United Kingdom. *Epidemiology and Infection* 2005; **133**: 575–582.
32. **Grundmann H, *et al.*** The dynamic changes of dominant clones of *Staphylococcus aureus* causing bloodstream infections in the European region: results of a second structured survey. *Eurosurveillance* 2014; **19**: pii 20987.
33. **Bassetti S, Battegay M.** *Staphylococcus aureus* infections in injection drug users: risk factors and prevention strategies. *Infection* 2004; **32**: 163–169.

https://doi.org/10.1017/S095026881500271X Published online by Cambridge University Press