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Severe illness and death among injecting drug users in Scotland: a case-control study

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SUMMARY

Between April and September 2000, 60 injecting drug users in Scotland died or were hospitalized with severe illness. Laboratory investigations suggested that *Clostridium novyi* and other bacteria were important aetiological agents. To determine associated environmental/behavioural factors a case-control study was undertaken with 19 'definite' and 32 'probable' cases in Glasgow, Scotland. For every deceased case ($n=19$), up to three proxy individuals were interviewed. Three controls were identified for each case. Multivariate logistic regression analyses compared (i) all cases and controls; (ii) definite cases and matched controls; (iii) probable cases and matched controls. In all three analyses injecting into muscle or skin and injecting most of the time with a filter used by someone else were the variables most strongly associated with illness. Comparing only muscle-injecting cases and controls, cases were significantly more likely to have injected larger amounts of heroin per average injection than were controls. The findings make an important epidemiological contribution to the understanding of the public health and clinical implications of the contamination of illicit drugs by histotoxic clostridia.

INTRODUCTION

Between April and September 2000 in Scotland, a severe unexplained illness occurred among 60 injecting drug users (IDUs), 23 of whom died. Over a similar period, 23 and 25 cases, of whom a total of 21 died, were also identified in Ireland and England respectively. These cases were characterized by severe inflammation at or near an injecting site often in association with multi-organ failure [1–5]. Soft-tissue infections (abscesses and cellulitis) are common among IDUs [6–9] and toxigenic forms of staphylococcus and streptococcus have been associated with necrotizing faciitis [10, 11] and other severe illnesses among drug users [12–14]; however, the incidence, severity and unusual characteristics of disease observed over a short period was unique to the experience of the observers.

Most cases ($n=50$) resided in the Greater Glasgow Health Board area of Scotland. At the beginning of May 2000 three cases presented, all from the south

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side of the city. By the middle of May, 13 IDUs from the same area had been hospitalized and, of these, six had died. Most of those affected were female and most had injected intramuscularly. These findings suggested that the illness was confined to one area of Glasgow and possibly one group of IDUs; by the end of May, however, cases had been identified among IDUs residing in various, but not all, areas of high drug use in the city. Cases had also been identified in areas of Scotland outside Glasgow.

In early May, a multidisciplinary team was established to investigate the problem and implement public health interventions [1–3]; its functions included the implementation of active surveillance to detect unreported cases, the coordination of specimen collection for laboratory analysis and the dissemination of information about the outbreak to the public health, clinical and IDU communities to optimize case detection and prevention.

By the middle of June 2000, laboratory investigations suggested that *Clostridium novyi* and other bacteria were important agents in the aetiology of the disease [15]; however, to determine, with confidence, the associated environmental/behavioural factors it was necessary to undertake a robust epidemiological investigation. An understanding of these would help prevent further cases both nationally and internationally. This paper reports the findings of this investigation.

METHOD

Study design

A case-control study was conducted between 3 June and 31 July 2000. The following hypotheses to explain the syndrome were generated by examining case histories of the initial cases: (i) that a batch of heroin, or an acidic substance used to dissolve it, had been contaminated with an as yet unknown organism; (ii) that the aforementioned batch of heroin required larger than usual amounts of acidic dissolver, thus causing even more tissue and muscle damage than normal which would favour growth of anaerobic bacteria to flourish at or in the injection site; and (iii) IDUs who injected intramuscularly or subcutaneously rather than intravenously were more likely to be affected.

Case definition

Cases were defined as IDUs in Scotland who (1) had presented to hospital since 1 April 2000 with significant inflammation at an injecting site; (2) had a severe inflammatory process at or around the injecting site; (3) had a severe systemic reaction, characterized by hypotension, a leukaemoid reaction, necrotizing fasciitis and evidence of multi-organ failure; and (4) had died outside of hospital and had post-mortem findings suggestive of septic or toxic shock. Cases fulfilling criteria [(1)+(2)] plus [(3) or (4)] were labelled 'definite', while those satisfying (1)+[(2) or (3) or (4)] were considered 'probable'.

Case-patients and surrogates for deceased case-patients: recruitment

Patients were interviewed using a standardized questionnaire (see below). To provide information on the drug usage of each deceased case-patient, up to three surrogates who claimed to know the deceased person's drug habits during the 2 months before hospitalization or death were interviewed. If a deceased case-patient's sexual partner was also an IDU, the partner was probably familiar with the injecting habits of the deceased; accordingly, such partners were sought as optimal surrogates. If IDU sexual partners could not be identified, friends or relatives who had injected with the deceased patient during the 2 months before hospitalization were interviewed. If members of these groups were unavailable or unwilling to be interviewed, non-injecting friends or relatives who were close to the deceased were considered. To recruit surrogates for deceased cases, the next-of-kin was contacted by the interview team and asked to nominate three potential surrogates. Interviews with patients or surrogates were conducted by two interviewers either in hospital or in the patient's or surrogate's homes.

Controls: eligibility criteria

Controls were required to be within the age range of cases (16–50 years); to have injected illicit drugs intravenously and/or subcutaneously or intramuscularly during the 2 months prior to interview; not to have experienced symptoms consistent with the case-defining criteria; and to reside in the postcode areas in which cases had resided. Whilst IDUs sometimes purchase heroin in areas outside of their own residence, not all areas of high drug use in the city had cases. It was assumed that the presumably contaminated heroin was circulating in those areas of the city where cases had been identified.

Controls: recruitment

Controls were recruited by a team of trained interviewers who travelled in a mobile caravan around the areas of the city where cases had resided at the time of illness. At street sites, the interviewers approached individuals, explained the nature of the investigation to them and, subject to their eligibility for entry into the study, asked them if they would consent to an interview. Interviews were conducted in the mobile caravan. Participants were offered a can of juice and a chocolate bar for their time.

Questionnaire

The questionnaire was administered by experienced interviewers and took 40–50 min to complete. After eligibility, questions followed on demographic characteristics; drug preparation techniques (including type and amounts of acidic dissolver used) and injection practices (including skin-cleaning procedures); sharing of drugs and sharing, storage and re-use of injecting paraphernalia; routes, characteristics and amounts of drugs injected; source of heroin used (single *vs*. multiple unidentified dealers); and recent illnesses. Questions applied to experience and behaviours in the previous 2 months.

All respondents were assured of the anonymous and confidential nature of the study; the only identifiers collected were initials, gender, date of birth and area of residence. These identifiers were used only to eliminate duplicate interviews amongst the control group. At the time the study was undertaken it was possible that criminal proceedings might arise from the overall investigations. Despite the lack of personal identifiers collected during interview, case and control respondents were considered more likely to provide truthful answers only if the respondents could be assured that their responses would not be used to incriminate them. Accordingly, the police and prosecution service in Glasgow agreed that no completed questionnaire would be used in any part of the criminal investigation. In addition, to maximize the validity of responses and the safety of the interviewers, questions seeking to identify individual dealers or sources of a specific batch of heroin were not raised.

As one of the considered hypotheses was the excessive use of 'larger than usual' amounts of an acidic substance to dissolve heroin, it was important to measure as objectively as possible how much respondents were using. IDUs referred to the amount of dissolver used in terms of numbers of 'pinches' (one pinch being an amount picked up between forefinger and thumb). Each IDU was asked to demonstrate what they classed as a 'pinch'. Citric acid (the dissolver most commonly used by IDUs in Glasgow) was not available to the interviewers at the time of the study. During the outbreak there was concern that citric acid was a causal agent in the illness. As a result, retailers removed citric acid from sale. In the absence of citric acid, interviewers offered salt as a substitute. Each IDU picked up a 'pinch' of salt and deposited it into a small bag which was then weighed. Respondents were then asked to estimate the average number of pinches they had used to dissolve heroin in any one batch in the previous 2 months and the maximum amount of citric acid used was calculated from that.

Data analysis

Since matching on neighbourhood of residence was critical to the study design, only cases and controls matched by the postcode area of residence were included in the analysis. Unadjusted univariate and adjusted multivariate logistic regression analyses were used to compare: (*a*) all cases with matched controls; (*b*) definite cases with matched controls; (*c*) probable cases with matched controls; (*d*) all case and control respondents who had injected into muscle in the 2 months prior to hospitalization (for cases) or prior to interview (for controls).

RESULTS

Sample size and characteristics

Fifty-three persons in and around Glasgow who met the case definition were enrolled into the study; the earliest case hospitalization date was 19 April and the latest 31 July 2000. Of these, 20 and 33 met the definite and probable case-definitions respectively; 17 definite and three probable cases had died before this study commenced.

Data were collected from 32 out of 33 (97%) living (3 definite and 29 probable), and from 26 surrogates for 18 out of 20 (90%) deceased (16 definite and 2 probable), cases. Of the three cases from whom no interview data were obtained, two were deceased and no surrogates could be identified, and the other could not be contacted. Two deceased cases each had three surrogates; four cases each had two; and 12 cases each had a single identified surrogate for interview.

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Table 1. *Drug-using behaviours of Scottish cases, who either died or were hospitalized with unexplained severe illness between April and July 2000, compared to controls, who were recruited in areas where cases reside: conditional (matched respondents) logistic regression analyses*

Responses at interview (for the period in the previous 2 months)*	Matched respondents: Cases ($N_1=33$) n_1 (% of N_1)	Matched respondents: Controls ($N_2=144$) n_2 (% of N_2)	Odds ratio (95% CI)† (Cases *vs.* Controls): Univariate	Odds ratio (95% CI)† (Cases *vs.* Controls): Multivariate
Gender				
Male	15 (45%)	108 (75%)	1·00	1·00
Female	18 (55%)	36 (25%)	**7·27 (2·64–20·0)**	**4·64 (1·00–21·80)**
Age (years)				
<25	5 (15%)	34 (24%)	1·00	1·00
25–29	9 (27%)	59 (41%)	0·97 (0·30–3·11)	
⩾30	19 (58%)	51 (35%)	2·21 (0·73–6·70)	**5·44 (1·44–20·63)**
Time since onset of injecting (years)				
<2	4 (13%)	23 (16%)	0·65 (0·18–2·33)	
2–5	7 (23%)	44 (31%)	0·80 (0·28–2·29)	n.s.
6–10	7 (23%)	28 (19%)	1·05 (0·37–2·97)	
⩾11	12 (40%)	49 (34%)	1·00	
Received prescribed methadone*				
Yes	10 (32%)	79 (55%)	**0·38 (0·16–0·91)**	n.s.
No	21 (68%)	65 (45%)	1·00	
Frequency of injecting heroin (times per day)*				
⩽1	9 (30%)	64 (45%)	1·00	
2–3	11 (37%)	53 (37%)	1·29 (0·50–3·29)	n.s.
⩾4	10 (33%)	25 (18%)	**2·87 (0·99–8·32)**	
Cocaine use*				
None	25 (83%)	84 (58%)	1·00	1·00
Used (not injected)	1 (3%)	31 (22%)	**0·23 (0·07–0·70)**	**0·15 (0·03–0·73)**
Injected	4 (13%)	29 (20%)		
Route of injection*				
Muscle	17 (53%)	18 (13%)	**12·48 (3·71–42·02)**	**18·30 (3·99–83·93)**
Skin (not muscle)	2 (6%)	2 (1%)	**12·02 (1·24–116·4)**	
Missed vein (not muscle or skin)	7 (22%)	66 (46%)	0·95 (0·28–3·19)	1·00
Vein only	6 (19%)	58 (40%)	1·00	
Maximum strength of heroin used‡*				
High	11 (38%)	37 (26%)	1·84 (0·77–4·38)	n.s.
Low-medium	18 (62%)	104 (74%)	1·00	
Colour of heroin used§*				
Light	8 (31%)	34 (24%)	1·15 (0·44–3·02)	n.s.
Dark only	18 (69%)	106 (76%)	1·00	
Used citric acid to dissolve drugs*				
Yes	30 (94%)	142 (99%)	1·00	n.s.
No	2 (6%)	2 (1%)	3·80 (0·50–30·2)	
Maximum amount of citric acid used per injection (measured in grams of salt)*				
⩽0·1	7 (33%)	37 (29%)	1·00	n.s.
0·11–0·5	12 (57%)	75 (58%)	0·94 (0·32–2·75)	
0·51–2·0	2 (10%)	17 (13%)	0·61 (0·11–3·28)	
Extent to which heated drugs*				
Always bubbled	21 (70%)	105 (74%)	1·00	n.s.
Not always	9 (30%)	37 (26%)	1·16 (0·48–2·81)	

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Table 1 (*cont.*)

Responses at interview (for the period in the previous 2 months)*	Matched respondents: Cases ($N_1=33$) n_1 (% of N_1)	Matched respondents: Controls ($N_2=144$) n_2 (% of N_2)	Odds ratio (95% CI)† (Cases *vs.* Controls): Univariate	Odds ratio (95% CI)† (Cases *vs.* Controls): Multivariate
Wiped injection site with mediswab before injecting*				
Most of time	14 (44%)	53 (37%)	1·39 (0·55–3·53)	n.s.
⩽Half the time	7 (22%)	38 (27%)	0·90 (0·31–2·58)	
Never	11 (34%)	52 (36%)	1·00	
Washed hands before injecting*				
Most of time	3 (13%)	49 (34%)	0·29 (0·08–1·07)	n.s.
⩽Half the time	4 (17%)	28 (20%)	0·59 (0·18–1·93)	
Never	16 (70%)	65 (46%)	1·00	
Shared a needle/syringe‖*				
⩾Once a week	7 (23%)	8 (6%)	**5·63 (1·58–20·1)**	n.s.
<Once a week	2 (7%)	25 (17%)	0·40 (0·09–1·86)	
Never	21 (70%)	110 (77%)	1·00	
Shared a filter*				
Most of time	15 (50%)	21 (15%)	**15·28 (4·48–52·09)**	**21·40 (3·95–116·0)**
⩽Half the time	7 (23%)	37 (26%)	1·86 (0·60–5·89)	3·28 (0·61–17·71)
Never	8 (27%)	85 (59%)	1·00	1·00
Shared a spoon*				
Most of time	15 (52%)	40 (28%)	**2·54 (1·05–6·14)**	n.s.
⩽Half the time	4 (14%)	35 (25%)	0·70 (0·20–2·48)	
Never	10 (35%)	67 (47%)	1·00	
Flushed out needles/syringes in used water‖*				
Most of time	6 (20%)	23 (16%)	1·69 (0·58–4·88)	n.s.
⩽Half the time	6 (20%)	25 (18%)	1·20 (0·43–3·38)	
Never	18 (60%)	93 (66%)	1·00	

* Denotes responses at interview for the period in the previous 2 months.

† Results in bold are statistically significant at the 5% level; n.s., non-significant factors at the 5% level were not included in the multivariate regression model.

‡ Respondents were asked to assess the strength of the heroin they had used in the previous 2 months on a scale of 1–10, with 10 being the strongest; in the analyses, we have taken the maximum value reported by each respondent and categorized 'high' as scored 8–10 and 'low-medium' as scored 1–7.

§ Respondents were asked to assess the colour of the heroin they had used in the previous 2 months from a colour chart.

‖ Respondents were asked how often they had injected with equipment already used by *someone else* (including their partner).

Where numbers do not add up to 33 (cases) or 144 (controls), information was not reported.

For 11 deceased cases, at least one surrogate who injected drugs was interviewed.

When surrogates for two of the deceased gave conflicting information, responses from the surrogate who had spent the greatest amount of time with the case prior to death were used.

In total, 144 controls were recruited in postcode areas where 16 of the 19 definite and 17 of the 31 probable cases resided. Seventeen cases were excluded from the analyses as no controls, matched for postcode area were found. Six of these excluded cases resided outside the city limits and it was not possible to commit the necessary resources to recruit corresponding controls; for the remaining 11, attempts to recruit controls were unsuccessful.

All cases and matched controls (Table 1)

In the matched univariate analysis of cases and controls, factors positively associated with illness were: female gender, injecting heroin four or more times daily, injecting into muscle or skin, injecting at least

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Table 2. *Drug-using behaviours of definite cases compared to controls, for controls who were recruited in areas where 'definite' cases reside: conditional (matched respondents) logistic regression analyses*

Responses at interview (for the period in the previous 2 months)*	Matched respondents: Definites ($N_1=16$) n_1 (% of N_1)	Matched respondents: Controls ($N_2=112$) n_2 (% of N_2)	Odds ratio (95% CI)† (Definites *vs.* Controls): Univariate	Odds ratio (95% CI)† (Definites *vs.* Controls): Multivariate
Gender				
Male	7 (44%)	80 (71%)	1·00	n.s.
Female	9 (56%)	32 (29%)	**7·00 (1·73–28·30)**	
Age (years)				
<25	3 (19%)	26 (23%)	1·00	n.s.
25–29	5 (31%)	43 (38%)	0·90 (0·20–4·10)	
⩾30	8 (50%)	43 (38%)	1·42 (0·34–6·02)	
Time since onset of injecting (years)				
<2	2 (15%)	16 (14%)	1·43 (0·21–9·57)	n.s.
2–5	5 (39%)	35 (31%)	1·84 (0·38–9·00)	
6–10	3 (23%)	24 (21%)	1·41 (0·27–7·36)	
⩾11	3 (23%)	37 (33%)	1·00	
Received prescribed methadone*				
Yes	2 (14%)	65 (58%)	**0·12 (0·03–0·58)**	**0·04 (0·002–0·79)**
No	12 (86%)	47 (42%)	1·00	1·00
Frequency of injecting heroin (times per day)*				
⩽1	4 (31%)	50 (46%)	1·00	n.s.
2–3	3 (23%)	40 (36%)	0·82 (0·18–3·82)	
⩾4	6 (46%)	20 (18%)	3·14 (0·75–13·22)	
Cocaine use*				
None	13 (100%)	70 (62%)	Not tested	
Used	0 (0%)	42 (38%)		
Route of injection*				
Muscle	12 (75%)	16 (14%)	**26·30 (5·66–122·0)**	**57·92 (4·35–771·7)**
Skin (not muscle)	1 (6%)	2 (2%)		
Missed vein (not muscle or skin)	3 (19%)	47 (42%)	1·00	1·00
Vein only	0 (0%)	47 (42%)		
Maximum strength of heroin used‡*				
High	6 (50%)	27 (25%)	2·94 (0·84–10·20)	n.s.
Low-medium	6 (50%)	82 (75%)	1·00	
Colour of heroin used§*				
Light	5 (56%)	26 (24%)	2·98 (0·68–13·20)	n.s.
Dark only	4 (44%)	82 (76%)	1·00	
Used citric acid to dissolve drugs*				
Yes	15 (100%)	111 (99%)	Not tested	
No	0 (0%)	1 (1%)		
Maximum amount of citric acid used per injection (measured in grams of salt)*				
⩽0·1	1 (17%)	30 (29%)	1·00	n.s.
0·11–0·5	5 (83%)	61 (59%)	2·43 (0·27–22·20)	
0·51–2·0	0 (0%)	12 (12%)		
Extent to which heated drugs*				
Always bubbled	10 (77%)	81 (74%)	1·00	n.s.
<Always	3 (23%)	29 (26%)	0·78 (0·19–3·16)	
Wiped injection site with mediswab before injecting*				
Most of time	6 (40%)	42 (38%)	1·38 (0·36–5·29)	n.s.

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Table 2 (*cont.*)

Responses at interview (for the period in the previous 2 months)*	Matched respondents: Definites ($N_1=16$) n_1 (% of N_1)	Matched respondents: Controls ($N_2=112$) n_2 (% of N_2)	Odds ratio (95% CI)† (Definites *vs.* Controls): Univariate	Odds ratio (95% CI)† (Definites *vs.* Controls): Multivariate
⩽Half the time	4 (27%)	30 (27%)	1·00 (0·2–4·29)	
Never	5 (33%)	39 (35%)	1·00	
Washed hands before injecting*				
Most of time	1 (11%)	42 (38%)	0·21 (0·02–1·82)	
⩽Half the time	2 (22%)	20 (18%)	0·77 (0·14–4·13)	n.s.
Never	6 (67%)	49 (44%)	1·00	
Shared a needle/syringe*				
⩾Once a week	4 (31%)	7 (6%)	**5·90 (1·26–27·75)**	
<Once a week	1 (8%)	18 (16%)	0·65 (0·07–5·63)	n.s.
Never	8 (62%)	86 (77%)	1·00	
Shared a filter‖*				
Mostly	7 (54%)	18 (16%)	**21·00 (2·59–170·0)**	**33·98 (1·95–593·0)**
⩽Half the time	5 (38%)	25 (23%)		
Never	1 (8%)	68 (61%)	1·00	1·00
Shared a spoon‖*				
Mostly	8 (67%)	31 (28%)	**13·22 (1·61–108·6)**	
⩽Half the time	3 (25%)	23 (21%)	7·11 (0·69–73·1)	n.s.
Never	1 (8%)	56 (51%)	1·00	
Flushed out needles/syringes in used water‖*				
Mostly	4 (31%)	19 (17%)	**3·40 (1·06–10·90)**	n.s.
⩽Half the time	4 (31%)	17 (15%)		
Never	5 (39%)	75 (68%)	1·00	

* Denotes responses at interview for the period in the previous 2 months.

† Results in bold are statistically significant at the 5% level; n.s., non-significant factors at the 5% level were not included in the multivariate regression model.

‡ Respondents were asked to assess the strength of the heroin they had used in the previous 2 months on a scale of 1–10, with 10 being the strongest; in the analyses, we have taken the maximum value reported by each respondent and categorized 'high' as scored 8–10 and 'low-medium' as scored 1–7.

§ Respondents were asked to assess the colour of the heroin they had used in the previous 2 months from a colour chart.

‖ Respondents were asked how often they had injected with equipment already used *by someone else* (including their partner).

Where numbers do not add up to 33 (cases) or 144 (controls), information was not reported.

once a week with a needle/syringe previously used by someone else, and injecting most of the time with a filter or spoon already used by someone else in the 2 months prior to interview. Cocaine use and having received prescribed methadone in the 2 months prior to interview were inversely associated with illness.

In the matched multivariate analysis, the factors positively associated with illness were: female gender, age ⩾30 years, having injected into muscle or skin and having injected most of the time with a filter used by someone else; the latter two behaviours were strongly associated with illness, as demonstrated by their odds ratios of 18·30 and 21·40 respectively (Table 1). Cocaine use was inversely associated with illness.

Length of injecting career, strength of heroin used, colour of heroin used, amount of citric acid used [no information for 12 out of 33 (36%) cases], cleaning of injecting site before injecting and flushing out needles and syringes in water used by someone else were not found to be related to illness. Other factors, not presented in the table and not significantly associated with illness, were re-use of own filter [24/31 (77% of matched cases) *vs.* 94/143 (66% of controls)] and use of heroin purchased in specific parts of Glasgow.

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Table 3. *Drug-using behaviours of cases compared to controls, amongst those who had reported injecting into muscle during the period at risk: unconditional logistic regression analyses*

Responses at interview (for the period in the previous 2 months)*	Cases ($N_1=27$) n_1 (% of N_1)	Controls ($N_2=18$) n_2 (% of N_2)	Odds ratio (95% CI)† (Cases *vs.* Controls)	
			Univariate	Multivariate
Gender				
Male	8 (30%)	10 (56%)	1·00	
Female	19 (70%)	8 (44%)	2·97 (0·86–10·30)	n.s.
Age (years)				
<25	4 (15%)	3 (17%)	1·00	
25–29	10 (37%)	10 (56%)	0·75 (0·13–4·25)	n.s.
⩾30	13 (48%)	5 (28%)	1·95 (0·32–12·0)	
Time since onset of injecting (years)				
<2	3 (13%)	2 (11%)	1·17 (0·15–9·00)	
2–5	9 (38%)	5 (28%)	1·40 (0·32–6·10)	n.s.
6–10	3 (13%)	4 (22%)	0·58 (0·10–3·51)	
⩾11	9 (38%)	7 (39%)	1·00	
Received prescribed methadone*				
Yes	7 (29%)	12 (67%)	**0·21 (0·06–0·77)**	n.s.
No	17 (71%)	6 (33%)	1·00	
Frequency of injecting heroin (times per day)*				
⩽1	5 (21%)	8 (44%)	1·00	
2–3	8 (33%)	6 (33%)	2·13 (0·46–9·94)	n.s.
⩾4	11 (46%)	4 (22%)	4·40 (0·89–21·8)	
Maximum number of times injected into the same muscle				
1–2	6 (40%)	7 (44%)	1·00	
3+	9 (60%)	9 (56%)	1·17 (0·28–4·87)	n.s.
Cocaine use*				
None	21 (91%)	8 (44%)	1·00	1·00
Used (not injected)	0 (0%)	9 (50%)	**0·08 (0·01–0·42)**	**0·07 (0·01–0·52)**
Injected	2 (9%)	1 (6%)		
Time since onset of injecting into muscle (months)*				
>6	8 (42%)	12 (71%)	0·30 (0·08–1·21)	n.s.
⩽6	11 (58%)	5 (29%)	1·00	
Frequency of injecting into muscle (times per week)*				
>3	11 (50%)	6 (33%)	2·00 (0·55–7·24)	n.s.
⩽3	11 (50%)	12 (67%)	1·00	
Average amount of heroin used per injection into muscle (grams)*				
0·2–0·5	15 (71%)	5 (28%)	**6·50 (1·60–26·35)**	**10·03 (1·68–59·96)**
<0·2	6 (29%)	13 (72%)	1·00	1·00
Maximum strength of heroin used‡*				
High	9 (41%)	5 (28%)	1·80 (0·47–6·84)	n.s.
Low-medium	13 (59%)	13 (72%)	1·00	
Colour of heroin used§*				
Light	7 (35%)	6 (38%)	0·90 (0·23–3·52)	n.s.
Dark only	13 (65%)	10 (62%)	1·00	
Used citric acid to dissolve drugs*				
Yes	25 (96%)	18 (100%)	Not tested	
No	1 (4%)	0 (0%)		

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Table 3 (*cont.*)

Responses at interview (for the period in the previous 2 months)*	Cases ($N_1=27$) n_1 (% of N_1)	Controls ($N_2=18$) n_2 (% of N_2)	Odds ratio (95% CI)† (Cases *vs.* Controls)	
			Univariate	Multivariate
Maximum amount of citric acid used per injection (measured in grams of salt)*				
⩽0·1	6 (50%)	5 (28%)	1·00	n.s.
0·11–0·5	5 (42%)	8 (50%)	0·45 (0·10–2·14)	
0·51–2·0	1 (8%)	3 (19%)		
Extent to which heated drugs*				
Always bubbled	17 (74%)	13 (72%)	1·00	n.s.
<Always	6 (26%)	5 (28%)	0·92 (0·23–3·68)	
Wiped injection site with mediswab before injecting*				
Most of time	8 (30%)	6 (33%)	1·89 (0·55–6·43)	n.s.
⩽Half the time	9 (35%)	3 (17%)		
Never	9 (35%)	9 (50%)	1·00	
Washed hands before injecting*				
Most of time	2 (12%)	7 (39%)	0·27 (0·07–1·09)	n.s.
⩽Half the time	3 (18%)	4 (22%)		
Never	12 (71%)	7 (39%)	1·00	
Shared a needle/syringe‖*				
⩾Once a week	5 (20%)	1 (6%)	1·22 (0·32–4·62)	n.s.
<Once a week	3 (12%)	4 (22%)		
Never	17 (68%)	13 (72%)	1·00	
Shared a filter‖*				
Most of time	12 (48%)	1 (6%)	**6·33 (1·66–24·24)**	n.s.
⩽Half the time	7 (28%)	5 (28%)		
Never	6 (24%)	12 (67%)	1·00	
Shared a spoon‖*				
Most of time	16 (67%)	6 (33%)	2·40 (0·65–8·89)	n.s.
⩽Half the time	2 (8%)	4 (22%)		
Never	6 (25%)	8 (44%)	1·00	
Flushed out needles/syringes in used water‖*				
Most of time	9 (36%)	3 (17%)	2·00 (0·58–6·85)	n.s.
⩽Half the time	5 (20%)	4 (22%)		
Never	11 (44%)	11 (61%)	1·00	

* Denotes responses at interview for the period in the previous 2 months.
† Results in bold are statistically significant at the 5% level; n.s., non-significant factors at the 5% level were not included in the multivariate regression model.
‡ Respondents were asked to assess the strength of the heroin they had used in the previous 2 months on a scale of 1–10, with 10 being the strongest; in the analyses, we have taken the maximum value reported by each respondent and categorized 'high' as scored 8–10 and 'low-medium' as scored 1–7.
§ Respondents were asked to assess the colour of the heroin they had used in the previous 2 months from a colour chart.
‖ Respondents were asked how often they had injected with equipment already used *by someone else* (including their partner).
Where numbers do not add up to 33 (cases) or 144 (controls), information was not reported.

Definite cases and matched controls (Table 2)

In the univariate analysis of definite cases *vs.* matched controls, injecting four or more times daily conveyed no additional risk; otherwise, the analysis detected the same risk factors as those identified in the univariate analysis of all cases and matched controls.

Multivariate analysis showed injecting intramuscularly or subcutaneously and using a filter previously used by someone else most of the time as the only

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variables to be significantly associated with illness. Use of prescribed methadone was inversely related to illness in both univariate and multivariate analyses.

Probable cases and matched controls

When multivariate analysis was limited to probable cases and matched controls, muscle or skin injection and sharing filters remained positively associated with illness (data not shown).

Cases and matched controls who had injected into muscle (Table 3)

The only significant factor positively associated with illness, in both univariate and multivariate analyses, was the average amount of heroin injected into muscle at any one time; cases were significantly more likely than controls (71% *vs.* 28% respectively) to have injected larger quantities (0·2–0·5 g). The total amount of heroin injected into muscle in the previous 2 months was found to be less predictive (OR 5·94, 95% CI 1·05–33·70, adjusted) than the average amount injected at any one time. Repeated injection into the same muscle was not found to be significant at univariate or multivariate level. Use of cocaine was found to be inversely associated with illness in both univariate and multivariate analysis. Not receiving prescribed methadone and injecting with a used filter were positively associated at the univariate, but not multivariate, level.

DISCUSSION

By the time the case-control study had been completed, *C. novyi* type A had been isolated from the tissues of eight definite and five probable cases. Further, the unusual clinical findings of extensive oedema at the injection site and leukaemoid reaction – apparent in nearly all definite cases – were consistent with *C. novyi* being the principal aetiological agent [15]. The case-control study findings support some, but not all, of the original hypotheses concerning the chain of events that led to severe illness in so many individuals.

It was postulated that a batch of heroin, or an acidic substance used to dissolve it, had been contaminated with a microorganism. The presence of a significant relationship between illness and the quantity of heroin, but not citric acid, injected intramuscularly is consistent with the former being the source of infection. *C. novyi* was not isolated from the nine heroin samples recovered from cases or associates which underwent microbiological analysis [15]; only small amounts of heroin (0·2–0·5 g), however, were available for each anaerobic culture study (H. Holmes, CDC, personal communication, 2001). Since illness was found to be associated with injections of 0·2–0·5 g of heroin more than four times daily, the microbiological content of the heroin was probably low; if so, larger quantities of heroin might have yielded positive results.

The absence of a relationship between the occurrence of illness and the amount of citric acid used to dissolve the heroin does not support the second hypothesis that 'larger than usual' amounts of acid were injected, thus causing even more tissue and muscle damage than normal which would favour growth of anaerobic bacteria to flourish at or in the injection site. It is possible, however, that the crudeness of the approach to estimate the amount of acid used by injectors and the small numbers of cases involved in this study component – due to the high fatality rate – influenced the results. Nevertheless, it remains plausible that the injection of 'normal amounts' of acid was a crucial factor in the disease process.

The third hypothesis – IDUs who injected intramuscularly or subcutaneously were more likely to be affected – was well supported by the finding of a high odds ratio on multivariate analysis for this behaviour. Skin popping has been strongly associated with IDU-associated soft-tissue infection involving anaerobic bacilli [16–18], staphylococci, streptococci [19], and abscesses lacking an identified microbiological cause [20, 21].

The highly significant association between sharing a filter, through which the heroin acid solution is drawn to eliminate impurities, and the occurrence of illness, suggests that this item of injecting paraphernalia might have harboured infection. As most cases had social or familial links with each other, it is possible that they either obtained microbiologically contaminated heroin or contaminated their heroin/acid solution through the use of a contaminated filter. Recent observational work, undertaken by some of the investigators and involving the use of video technology, has shown that filters can be re-used several times and are often used in batch preparation of drug solution that is then shared between groups of injectors [22]. Studies of IDU-associated abscesses, generally, have not found an association between drug paraphernalia sharing and infection [20, 21]; one

exception is an outbreak of *S. aureus* infection among cocaine IDUs [12]. There is evidence, however, of a link between the sharing of filters and the acquisition of HCV infection [23]. The finding that filters might have had a role to play in propagating this outbreak supports the argument that sterile filters, spoons and water, in addition to needles and syringes, should be made available to IDUs to prevent the transmission of infections among this population.

At all levels of univariate analysis, the receipt of methadone was associated with a significantly lower risk of illness. In two of the three multivariate analyses, however, this effect was lost when variables such as frequency of injecting were adjusted for. A recent evaluation of entrants into methadone maintenance in Glasgow demonstrated that those who remained on methadone were much less likely to inject drugs and share injecting equipment than those who discontinued it [24].

Cocaine users and injectors had a lower risk of illness even when confounders such as frequency of heroin injecting were accounted for. This observation, difficult to explain, might be related to cocaine and heroin users (predominantly the control population) having had different sources of heroin from those who injected heroin only (the cases) during the period of study.

The validity of some of the data collected may have been suboptimal; all were based on self-reports and, in many instances, reliance on surrogate sources was required. Inaccurate recall by surrogates of injecting behaviour could have biased risk estimates [25]. Despite these potential flaws, the findings presented in this report, together with the clinical and microbiological data reported elsewhere, are consistent with the following hypothesis: IDUs injected an acidic solution of street heroin, contaminated with spores of *C. novyi* type A (with or without other organisms or unidentified cofactors) either intramuscularly or subcutaneously. The acidic solution devitalized the tissue, thus favouring the propagation of anaerobic infection. Toxin production led to the development of a severe localized inflammatory reaction with marked oedema which, in some cases, was followed by a life-threatening systemic illness, characterized by hypotension, a leukaemoid reaction and necrotizing fasciitis [15].

Previously, most *C. novyi* (previously *C. oedematiens*) infections were associated with war-related injuries experienced during the early 20th century [26, 27]; *C. novyi* is also responsible for Black Disease [28–31], a condition seen in large herbivores. Since 2000, awareness among clinicians and microbiologists of the use of enhanced anaerobic culture for the isolation of fastidious anaerobes which cause severe soft-tissue inflammation in IDUs, has increased; reports which identified histotoxic clostridia, including *C. novyi*, as a cause of IDU-associated abscesses, have been published [32, 33]. These suggest that *C. novyi* may be a more common cause of IDU-associated soft-tissue infection than previously thought.

The data presented in this report make a significant epidemiological contribution to the understanding of the public health and clinical implications of the contamination of illicit drugs by histotoxic clostridia. Further investigation of the role of storing, re-using and sharing filters in the transmission of micro-organisms, in particular anaerobic ones, is required. The development of surveillance systems, nationally and internationally, to monitor the incidence of serious soft-tissue infections among IDUs, is essential; it is anticipated that a surveillance initiative, currently being introduced in Scotland to monitor severe unexplained illness among individuals requiring intensive care, will constitute an early warning system for outbreaks of serious infection among both IDUs and, in the context of bioterrorist activity, members of the general population.

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