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REVIEW ARTICLE
Soft tissue infections caused by spore-forming bacteria in injecting drug users in the United Kingdom

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SUMMARY

From 2000 to May 2004 there has been a marked increase in illness resulting from spore-forming bacteria in injecting heroin users in the United Kingdom. *Clostridium novyi* caused 63 cases of severe illness in 2000 and seven further cases from 2001. Wound botulism first occurred in 2000 (six cases) with 51 further cases to March 2004. Tetanus occurred in 20 cases between late 2003 and March 2004. Infections with *C. histolyticum* (nine cases), *C. sordellii* (one case) and *Bacillus cereus* (one case) were also reported. The reasons for the increase in illness are unclear. The major risk factor was skin- or muscle-popping. The problem appears to be here to stay. This review describes the causative organisms, pathogenesis, clinical presentation, epidemiology and treatment of cases. Clinical vigilance and a high standard of anaerobic microbiology are essential. Clinicians and laboratories must report such cases (or likely cases) rapidly so that clusters can be rapidly identified, in order to control disease. Prevention relies on tetanus immunization.

INTRODUCTION

Opiates (heroin) and stimulants (cocaine and amphetamine) are the most widely injected psychotropic drugs and are administered by intravenous, subcutaneous (skin-popping) or intramuscular (muscle-popping) routes [1]. In the United Kingdom between 2000 and May 2004 there was a dramatic increase in cases of illness in injecting drug users (IDUs) caused by soft tissue infection with spore-forming bacteria (*Clostridium* and *Bacillus* spp.) (see Table). *Clostridium novyi* caused an outbreak of severe illness in IDUs in 2000, and a small number of cases since then. The first cases of wound botulism in IDUs occurred in 2000, and cases continued to occur. Cases of tetanus in IDUs increased dramatically from late 2003. A small number of infections with *C. sordellii, C. histolyticum* and *B. cereus* in IDUs were also reported. Gangrene associated with *C. perfringens* and *C. novyi* infection was a major source of mortality from wounds, particularly in warfare, before the advent of antibiotics. Thus, what is now seen in IDUs appears to be an old disease that has found a new niche. This review describes the aetiological agents, their sources, pathophsyiology, epidemiology, clinical presentation, clinical features and therapy of these illnesses in IDUs. All IDUs should be up to date with their tetanus boosters. Rapid reposting by clinicians

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Table. *Anaerobic and aerobic spore-forming bacteria associated with soft tissue infection in IDUs in the United Kingdom*

Organism	Date	No. of suspected or confirmed cases
Clostridium botulinum	2000	6
	2001	4
	2002	23
	2003	13
	2004 to March	11
Clostridium tetani	2003 to February 2004	20
Clostridium novyi	2000	63
	2001	5
	2002	0
	2003	1
	2004 to May	2
Clostridium sordellii	2001	1
Clostridium histolyticum	December 2003 to February 2004	9
Bacillus cereus	2001	1

and laboratories of such cases (or likely cases) will enable the extent of illness to be ascertained and clusters to be quickly identified. This will assist in disease control.

BACKGROUND

Infections in IDUs

Infections are the most frequent cause of hospitalization in IDUs [1]. Skin and soft tissue infections, such as cellulitis and abscesses, are a significant problem [2, 3]. Infections may be bacterial, viral, fungal or parasitic; mixed infections are common [1]. Acute and subacute infections are generally caused by bacteria [1] and may be mixed aerobic and anaerobic (>50%) or predominantly aerobic (such as *Staphylococcus aureus* and *Streptococcus* spp.) [3]. Chronic viral infections include human immunodeficiency virus, hepatitis B and C and human T-cell lymphotrophic virus-II. Fungal infections and malaria have also been reported in IDUs [1].

Source of the organisms

There are two main sources of organisms: the IDUs themselves (their oropharynx, skin or faeces), and the environment. Contamination may occur when the user prepares or injects the drug, uses shared needles or re-uses injection paraphernalia. Manufacturing and handling of heroin may be far from hygienic. Environmental contamination with spore-forming organisms may occur during the later stages of production (particularly when drying the drug), repackaging, 'cutting' (addition of bulking substances or other drugs) or distribution. One recognizes similarities with discussions on sources of clostridial spores in gas gangrene and myonecrosis in World Wars I and II [4]. Zeissler & Neller (quoted in ref. [4]) demonstrated that the relative incidence of different clostridial species in gangrene and soil was similar. The exception was gas gangrene in the Western Desert in World War II as that area was essentially free of clostridia, and the principal source of infection there was thought to be faecal contamination of soldiers' clothes [4].

The sudden increase in, and clustering of, cases of infection with *C. novyi*, *C. botulinum*, *C. tetani* and *C. histolyticum* suggested contamination of heroin at a common source rather than by individual users. *B. cereus* has been isolated from heroin [5–7]. *C. novyi* and *C. botulinum* were not isolated from 64 samples (each of ~0·1 g) of street heroin from the United Kingdom in 2000 [8], but was isolated from internal washings of used syringes from a wound botulism case [9]. Given the low number of cases of illness compared to the number of times heroin is injected, it is likely that if heroin is the source of infection, the level of contamination is low.

Risk factors: IDU behaviour

Injecting anaerobic bacterial spores intravenously will not provide an environment suitable for spore germination and multiplication of vegetative cells that produce the toxins. Skin- and muscle-popping lead to new 'niches' for microbial pathogens to fill and are major risk factors for the development of infections [1, 2, 10]. These injection routes may be used once intravenous injection is no longer possible or in preference to that route. Injection of drugs for longer periods of time is thought to correlate with the use of skin- and muscle-popping and, therefore, with more severe presentations of sepsis in IDUs [10]. The relationship between skin- and muscle-popping and disease mediated by spore-forming organisms echoes the words of Ogilvie (quoted in [4]): 'it is a disease associated with a particular opportunity rather than a particular organism'.

Heroin used in the United Kingdom is predominantly a powder. It is not readily soluble in water and is dissolved in 'mild' acid (e.g. lemon juice or citric acid) with gentle heat before injection. However 'mild' the acid, the pH may be ~2·5 [11]; this will kill non-spore-forming bacteria which can compete with spore formers. A concoction of heroin and citric acid heated in a spoon over a pilot light bubbled at 65–75 °C [11]. *C. novyi* spores isolated from a case in an IDU in 2000 were likely to survive the heating and acidification used to dissolve heroin [11]. In addition, this heat treatment will stimulate spores to germinate.

Heroin and cocaine injected together may induce soft tissue ischaemia [2]. Repeated injection of dilute acid and particulate debris into muscle will decrease muscle aerobicity, making conditions more favourable for growth of anaerobes. From all this it should be no surprise that illnesses caused by spore-forming bacteria are seen in IDUs. In the United Kingdom this has only occurred in any significant numbers since 2000 – the question is why?

Virulence factors

The *Clostridium* genus of anaerobic Gram-positive spore-forming bacilli contains several wound pathogens: *C. botulinum* and *C. tetani*, and the gas gangrene group of *C. perfringens*, *C. septicum*, *C. sordellii*, *C. novyi* and *C. histolyticum*. The *Bacillus* genus of aerobic Gram-positive spore-forming bacilli includes *B. cereus* and *B. anthracis*.

Clostridium and *Bacillus* spp. pathogenicity results from the production of potent toxins. *C. botulinum* and *C. tetani* produce neurotoxins that cleave one of three proteins required for the docking of vesicles containing acetylcholine at the neuromuscular junction [12, 13]. *C. novyi*, *C. perfringens*, *C. sordellii*, *C. histolyticum*, *B. anthracis* and *B. cereus* produce various histotoxins and cytotoxins. The α toxin of *C. novyi* is the major toxin in systemic pathogenesis and disrupts intracellular signalling and the cell cytoskeleton by glucosylating small GTPases of the Rho family [14]. *C. sordellii* produces two toxins that glucosylate small GTPases of the Rac and Ras family [14], a toxin with lecithinase and haemolytic activity, a collagenase and several proteases [15]. The α toxin (a phospholipase C) of *C. perfringens*, which is haemolytic, destroys platelets and leucocytes and increases capillary permeability, and with the θ toxin (perfringolysin O), a cholesterol-binding protein, are the major virulence factors in clostridial myonecrosis [16]. *C. histolyticum* and *C. septicum* produce α toxin which is haemolytic and necrotizing, collagenase, cytolysin and proteinases [15]. *C. septicum* [17] and *B. cereus* [18] produce a toxin which affects the cell cytoskeleton. *B. cereus* also produces cereulide, which affects mitochondrial metabolism [19].

These histotoxins diffuse rapidly and cause local and systemic damage. For example, in *C. novyi* and *C. sordellii* infection, severe soft tissue inflammation arises around the infection site with extensive oedema but minimal pus. Toxin spread via the blood stream results in severe systemic toxicity, a very high white blood cell (WBC) count, sustained low systolic blood pressure, shock and death. Post-mortem evidence of a diffuse toxic or infectious process is pleural effusions, soft tissue oedema and necrosis at the injection site.

ANAEROBIC NEUROTOXIN-PRODUCING SPORE-FORMING BACTERIA

Clostridium botulinum

In the United Kingdom the first cases of wound botulism presented in 2000 (six cases) and 2001 (four cases); numbers increased to 23 suspected cases in 2002 and 13 in 2003 ([9], HPA Food Safety Microbiology Laboratory (FSML), unpublished data) (Table). There has been an epidemic in IDUs in California, rising from one case annually in 1988 to 38 in 1999, and reports have increased elsewhere in the United States [20]. The reason for these increases is unclear; heroin used in California is black tar, a low grade resinous form primarily from Mexico and countries south of the United States, whereas that used in the United Kingdom is a powder, generally from Southwest Asia. Botulism has also followed intranasal and parenteral cocaine use [21].

The classical picture of botulism is of descending symmetrical flaccid paralysis with no fever. The clinical presentation of 33 of the 57 UK cases [22–25] and a case in Norway [26] did not always follow the clinical picture. Onset was between 2 and 14 days [9]. At least three cases had marked respiratory insufficiency and respiratory arrest before oculobulbar weakness and descending flaccid paralysis had developed fully. Ptosis and facial weakness were absent in at least one case on presentation, despite weakness in the neck and shoulders. Fever, thought to be due to respiratory infection, was present in at least two cases [9]. Abscesses were not detected in at least three

cases [9]. Accordingly debridement of recognized foci of infection may not remove the site causing botulism.

Cases should be treated immediately with antibiotics (metronidazole and either penicillin or clindamycin) and antitoxin. Prompt treatment with antitoxin on day 1 of symptoms resulted in a shorter period of ventilation and hospital stay in foodborne botulism cases [27]. The amount of botulinum toxin that causes illness is less than that needed to induce an immune response [28]. Patients had suffered two separate episodes of foodborne or wound botulism [20].

Clostridium tetani

Tetanus was first described in an IDU in 1876 [29]. Tetanus was uncommon in IDUs in the United Kingdom until 2003, with only two cases reported between 1984 and 2000 [30]. This changed markedly at the end of 2003, with 20 cases up to February 2004 [31]. In New York City between 1955 and 1965, 75% of all tetanus cases were in IDUs [32]. They comprised 1–2% of tetanus cases in the United States during the 1970s and 1980s [33] but 15–18% of cases between 1995 and 2000 [34]. This increase was largely due to cases in California, of whom 53% reported injecting black tar heroin [33, 34]. Skin-popping was a risk factor [32, 35].

Localized tetanus presents with local fixed muscle rigidity, enhanced deep tendon reflexes and painful spasms, all close to the site of injury, and can last months. It usually progresses, however, over ~ 2 weeks to generalized tetanus [36, 37]. Partial immunity may decrease the severity of illness.

The UK cases ranged from mild trismus to full-blown clinical tetanus. Most had severe tetanus needing mechanical ventilation; one patient died. Tetanus antibody levels and information on tetanus immunization status suggested inadequate protective immunity in most cases [30]. Most cases reported skin- or muscle-popping, consistent with the predominance of females and older injectors among cases. The lack of cases reported in Europe during 2003–2004 suggests that contamination of heroin occurred within the United Kingdom.

C. tetani is sensitive to metronidazole and penicillin; however penicillin is an antagonist of a neurotransmitter (gamma-aminobutyric acid) and, in theory, may act synergically with tetanus toxin to worsen muscular spasms [37]. Treatment should include debridement of the infection site, (if apparent), antibiotics (metronidazole and either clindamycin or penicillin) and administration of human anti-tetanus globulin. As with botulism, the amount of tetanus toxin is insufficient to induce immunity, so a patient who has recovered from tetanus requires prophylactic active immunization.

ANAEROBIC HISTOTOXIN-PRODUCING SPORE-FORMING ORGANISMS

Clostridium novyi

In 2000 there was a sudden increase in illness due to *C. novyi* in IDUs in Scotland, England and Ireland [38–40]. The outbreak lasted approximately 5 months. Only seven *C. novyi* isolates from IDUs have been referred to the Anaerobe Reference Laboratory (ARL) since then.

C. novyi produces a toxin-mediated disease with severe soft tissue inflammation around the site of infection which may include abscess formation, cellulitis, fasciitis, myositis, typically with extensive oedema but minimal pus, and sudden onset of shock. In the 2000 cluster, injection site inflammation, gross oedema but no pus, cellulitis and necrotizing fasciitis were followed by sustained low systolic blood pressure (<90 mmHg) despite fluid resuscitation leading to shock, collapse and death. The WBC count was grossly elevated (60×10^9/l). Of 23 definite cases in Scotland, 21 were known muscle-poppers; 20 of these 23 cases died; of 16 cases in Scotland 14 had generalized lower limb swelling or tissue oedema; 13 had large pleural effusions and 15 had necrotizing fasciitis. Deterioration was frequently dramatic: in those who died, the median time to death was 4 days after onset of symptoms [38–40]. The purity of heroin was 60–80% compared to the normal concentration of 30–40% and required more acid to dissolve it, which may have contributed to the severity of disease.

Treatment includes immediate debridement, antibiotic treatment with metronidazole and either clindamycin (which penetrates well into damaged tissue and also inhibits protein, i.e. toxin, synthesis) or penicillin and systemic support. There is no antitoxin available for human use and patients died in the 2000 cluster despite debridement, antibiotics and intensive care.

Clostridium histolyticum

Infection with *C. histolyticum* is rare and generally results in localized necrosis, not serious systemic

disease [4]. Isolates from nine cases of infection in IDUs were referred to the ARL between December 2003 and February 2004 [41]. Detailed clinical information on seven cases was not available to the authors so it is unclear whether the isolates were simple contaminants or whether there was abundant production of toxins and myonecrosis. Information was available for two persons in Glasgow. Both were muscle-poppers; one had bilateral buttock abscesses and the other a forearm abscess. These were not severe soft tissue infections. Both were treated successfully with surgical incision and appropriate antibiotics.

Clostridium sordellii

Since 2000 one case of illness due to *C. sordellii* has been reported in the United Kingdom, from Glasgow in 2001. The patient had 'muscle-popped'. A cluster of nine cases in IDUs presented with necrotizing fasciitis in California between December 1999 and April 2000. At least seven of these cases injected subcutaneously and *C. sordellii* was isolated from six cases [42].

Clinical features of *C. sordellii* infection include oedema, leukaemoid reaction and haemoconcentration with no fever, followed by shock and multi-organ failure [43], similar to *C. novyi* infection [38].

The Scottish patient presented with a 24-h history of minor groin pain, painful inguinal lymph nodes, a large buttock abscess, associated with cellulitis. He was afebrile and his WBC count was $23{\cdot}8 \times 10^9$/l. He received intravenous benzylpenicillin, metronidazole, flucloxacillin and clindamycin. An ultrasound of his buttock revealed marked tissue oedema but no obvious collection of pus. Within 48 h he deteriorated: WBC peaked at $58{\cdot}8 \times 10^9$/l and haemoglobin increased from 14·5 to 19 g/dl. Surgical debridement revealed 'solid oedema' of his thigh/buttock, patches of necrotic skin and necrotic fat and muscle in the gluteal region extending from his back at T10 to his knee. He was too unstable for full debridement. He had coagulopathy, hypotension and hypovolaemia and a large left-sided pleural effusion. For 48 h after debridement he was apparently successfully supported and was extubated. Over the subsequent 48 h he deteriorated and died, with increasing hypotension (refractory to inotropic support) and renal failure, hypothermia, adult respiratory distress syndrome and coagulopathy. His back and arms became oedematous. The median time in the nine US cases between onset of symptoms and admission was 3·5 days. All cases were afebrile at presentation. The median WBC count was $54{\cdot}3 \times 10^9$/l in the four patients who died and $23{\cdot}3 \times 10^9$/l in the survivors.

AEROBIC TOXIN-PRODUCING SPORE-FORMING ORGANISMS

Bacillus cereus

B. cereus has been implicated in serious infections in IDUs [5, 6] and causes a gangrene-like syndrome that may be confused with clostridial infection. A recent report described an IDU who skin- and muscle-popped. He presented with malaise, vomiting, dysnopea, apyrexia, low blood pressure, a tender liver edge, leukocytosis and neutrophilia. The injection site was erythrematous, indurated and tender but there was no evidence of fluctuance or crepitus. The patient made a full recovery following antibiotic therapy and debridement [7]. *B. cereus* was isolated from a fine- needle aspirate from the swollen forearm, but not from tissue. An isolate of *B. cereus* from heroin used by the patient was indistinguishable from a clinical isolate by amplified fragment length polymorphism [7].

Bacillus anthracis

In 2000, in addition to a case of wound botulism, another 'skin-popper' in Norway presented with a 4-day history of infection in his buttock, which was excised. He was given dicloxacillin and discharged. He was readmitted 4 days layer in cardiovascular shock. He was still afebrile. The CSF was bloody and purulent and contained Gram-positive rods bacilli without endospores. The WBC count was 5×10^9/l in CSF and $25{\cdot}6 \times 10^9$/l in serum. *B. anthracis* was isolated from serum. Surgical exploration of his buttock, thigh and lower abdominal wall revealed massive oedema of muscles and subcutaneous tissues, but no pus or necrosis. He died shortly afterwards [44]. In many respects the clinical presentation, cause and pathogenesis was very similar to the cases of *C. novyi* infection in Scotland in 2000, except that the organism was an aerobic Gram-positive species rather than an anaerobe.

LABORATORY TESTS

These agents require laboratory confirmation of the clinical diagnosis whenever possible. Botulinum

neurotoxin may be detected in serum (10 ml) or pus and the toxin type (A–G) determined. The organism may be isolated from wound or tissue samples. Routine laboratory tests are not helpful and specimens must be sent to a reference laboratory, which in the United Kingdom is the HPA FSML. Tetanus toxin can be detected in serum (10 ml; in the United Kingdom, FSML, HPA Colindale). A tetanus antibody level below the protective level (in the United Kingdom, test performed at the Respiratory and Systemic Infection Laboratory (RSIL), HPA Colindale or locally) is supportive of the clinical diagnosis. Organisms isolated from wound tissue should be sent to a reference laboratory for confirmation (the ARL in the United Kingdom) and for toxigenicity tests (FSML in the United Kingdom). Culture of more fastidious anaerobes such as *C. novyi* and *C. sordellii* require care in specimen transport and prolonged incubation (up to 2 weeks) in a quality-controlled anaerobic environment. Factors important in the isolation and identification of clostridia are discussed in Brazier et al. [45].

B. cereus isolates should be referred to a reference laboratory (FSML in the United Kingdom) for confirmation and typing. In cases of suspected anthrax a reference laboratory should be contacted immediately – Specialist and Reference Microbiology Division (SRMD), HPA Porton Down in the United Kingdom. *B. anthracis* is a Hazard Group 3 organism; all work on suspect cultures must be performed in a microbiological safety cabinet in a containment level 3 room. If *B. anthracis* is suspected clinically, specimens should be referred directly to a reference laboratory and cultured in parallel.

PREVENTION AND REDUCTION OF BACTERIAL COMPLICATIONS OF INJECTING DRUG USE

The most effective way to reduce infection is to stop the injection of drugs, particularly skin- or muscle-popping, which are major risk factors. Reducing needle sharing and re-use of injection equipment should reduce transmission of infections between IDUs. Cleaning skin with alcohol before injection was significantly protective against abscesses caused by skin and mouth flora [2]. Cleaning skin or using clean paraphernalia did not decrease the risk of botulism [46], which suggests that the source of *C. botulinum* is heroin or substances added to it, and not the user's skin. This may also be true for other spore-forming organisms.

Advice against skin- and muscle-popping, early recognition and publicity about potentially 'rogue' batches of heroin, and clinical awareness of the problem are all important for control. Health professionals should ask IDUs about their tetanus immunization status. IDUs who have not received five doses of tetanus-containing vaccine or are unsure about their vaccination status should be offered additional tetanus-low dose diphtheria (Td) vaccination. Many IDUs will require at least one booster [30]. Unvaccinated IDUs should be encouraged to complete a primary course of Td vaccination followed by two further boosters. IDUs might benefit from regular boosters to ensure protection from ongoing contamination of heroin.

CONCLUSIONS

We describe here the United Kingdom experience of serious disease in IDUs caused by various spore-forming organisms and associated with skin- and muscle-popping. The picture, however, is still an emerging one. The reason for the increase in illness is unclear. It is highly likely that if IDUs continue the practice of skin- and muscle-popping, and the manufacture and distribution of heroin continues in the same unhygienic fashion, the problem is here to stay. The question must be asked 'What has changed in heroin supply and use since the end of 1999?' It remains unanswered.

Important practice points

- It is crucial that front-line clinicians have a high index of clinical suspicion in IDUs who skin/muscle-pop. Clinicians should be aware of the different clinical presentations (some of which may be atypical, noting that they often result from the effect of a specific toxin(s).
- Careful examination of the patient is most important to elicit neurological signs and to find evidence of abscess/soft tissue infections that may be occult. Radiological investigations such as ultrasonography, CT and MRI scans may be helpful but necrotizing fasciitis is often difficult to diagnose even in non-IDUs and there is no substitute for careful surgical inspection in suspicious cases [3, 38].
- A soft tissue source should be carefully sought even in cases of wound botulism and tetanus and, if

found, debrided. However, the site of infection may be very small and contain no pus.

- The finding of a WBC count greater than 30×10^9/l with tissue oedema and/or large pleural effusions should alert clinicians to the possibility of histotoxin-producing clostridia (such as *C. novyi* or *C. sordellii*) as the aetiological agent [38].
- Treatment should be aimed at 'removing the opportunity' for these organisms to produce toxins. Inevitably this means that early, aggressive and often repeated surgical debridement is most important, particularly with severe soft tissue infection (SSTI). However, in a large proportion of SSTI cases caused by *C. novyi* in 2000, early and aggressive surgical debridement with appropriate antimicrobial therapy failed to prevent death.
- Antimicrobial therapy is only an adjunct but should be appropriate and include anti-anaerobic cover with metronidazole and either clindamycin or penicillin. Clindamycin is anti-anaerobic and has good activity against Group A β-haemolytic streptococci and methicillin-sensitive *S. aureus* – both major causes of soft tissue infections in IDUs. Suitable cover must also be given against Gram-negative aerobes; an aminoglycoside may be included to provide this cover and to act synergistically with penicillins active against both staphylococci and streptococci [4, 38].
- Blood cultures should be taken prior to administration of any antimicrobial agents. In infections caused by *B. anthracis*, cultures are likely to be positive before but not after the first dose of an antimicrobial [38]; in clostridial intoxications, blood cultures will be negative.
- It is essential that good anaerobic techniques are employed. These include heat shock to select for spores and prolonged incubation (for up to 2 weeks) to isolate low numbers of these strict anaerobes [45].
- There is a crucial role for reference laboratories in confirmation of botulism and tetanus and in speciation of non-perfringens clostridia.
- There is an obvious need for prompt accurate reporting of probable cases to appropriate local and national public health authorities, in order to identify clusters/outbreaks of disease. There may be a role for national syndromic surveillance of unusual illnesses.
- IDUs who have not received five doses of tetanus-containing vaccine, or are unsure about their vaccination status, should be offered additional tetanus-low dose diphtheria (Td) vaccination.

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