



Advice for doctors on diagnosis, management and reporting
Severe systemic sepsis related to soft tissue inflammation in
injecting drug users
Health Protection Agency
July 2008

1. Introduction

This document has been produced as part of a public health alert in response to two cases of *Clostridium novyi* infection in injecting drug users since June 2008, in Kent and Essex, with one case a fatality.

It describes the previous cluster of cases of severe systemic sepsis related to soft tissue inflammation in injecting drug users that were identified in Scotland, Ireland, England and Wales between April 1st and August 1st 2000 – as background on the potential risks.

It updates advice to doctors for diagnosis, management and reporting of such cases.

2. Background.

In mid-April 2000 a cluster of severe illness and death in injecting drug users was identified in Glasgow. Subsequent active case finding revealed a second cluster of cases in Dublin and also detected cases scattered throughout England and Wales, though primarily clustered in the North West around Manchester and Liverpool.

Between April 1st and August 1st 2000, a total of 104 probable or definite cases were identified in Scotland, Ireland, England and Wales, 37 of which met the most stringent case definition which has been used to focus microbiological investigation. Of these cases 35 died. The clinical course of those proceeding to death was usually rapid and was consistent with infection by a toxin producing micro-organism. Microbiological investigations revealed a range of anaerobic *Clostridium* species in cases including *Clostridium novyi*, *Clostridium tetani* and *Clostridium botulinum* all of which produce powerful toxins. *Clostridium* species have long been recognised to produce similar illness in animals, and several were important causes of gas gangrene arising from traumatic wounds in soldiers, particularly during the First World War. The syndrome in 2000/2001 had not been previously seen in injecting drug users.

Simultaneous with that outbreak there were also several cases of wound botulism and tetanus in injecting drug users in England and Scotland. It was considered that it may have been that some of the heroin in circulation during the time of that outbreak was generally contaminated with a number of *Clostridium* species resulting in a range of clinical effects. The investigating teams in Glasgow and Dublin conducted case control studies to explore the possible role of risk factors other than the heroin itself (e.g. the method of preparation, materials used to inject and any other drugs co-injected). Although several of the cases were HIV positive, and rather more were hepatitis C positive, the cases did not appear to have been particularly immunosuppressed.

Surveillance of cases continued until the end of 2000 in England and Scotland and very few further reports were subsequently received. It was possible that there may have been a particular batch of heroin that was contaminated with toxin producing clostridia but which had a limited route of distribution and which was largely used up or was removed from circulation.

Subsequently, there was concern in 2001 that part of the batch of heroin that may have been the source of the original outbreak, could again be in circulation, and in December 2003 to March 2004 a similar outbreak occurred due to *Clostridium histolyticum*.

Given the identification of two new cases close to each other since June 2008, continued vigilance is now required to detect, promptly treat, and report any further cases.

3. Case description

3.1 Local signs

Cases of this illness are characterised by local inflammation at a subcutaneous or intramuscular injection site. The local inflammatory reaction reported has varied considerably and not all of the following features are present in every case. Some cases have experienced only minimal pain and swelling at an injection site (usually the buttock, thigh or upper arm) while others have presented with severe local symptoms and signs; these include pain, widespread oedema (often extending far beyond the site of injection e.g. to involve a whole limb), myositis, and erythema/cellulitis or a bruised purplish appearance. Some lesions have been described as abscess-like but characteristically have produced little or no pus on incision/aspiration. Some have had a blackened/blistered area at the centre of the lesion. Others have had evidence of extensive necrosis and occasionally necrotising fasciitis has featured. Characteristically cases have not had high fevers associated with these lesions (i.e. their temperature is usually less than 40°C and may be normal or even low)

3.2 Systemic signs

Severe systemic features have usually occurred several days after development of the local lesion. There has then often been a dramatic deterioration in the patient's condition. Some cases have presented to hospital in a state of collapse rather than because of a local lesion, though such a lesion can be found on the patient. Most usually there is circulatory collapse with sustained hypotension (systolic < 90mmHg). Some cases develop adult respiratory distress syndrome, whilst others develop disseminated intravascular coagulation. At this stage, the patient may be hypothermic. All of these are likely to be toxin-mediated effects. By the time patients develop serious illness, deterioration to death is often inexorable despite antimicrobial and

surgical treatment and the patient's condition is not sustainably responsive to standard supportive measures. In most cases, however, the patient has remained mentally alert until an advanced stage. Another characteristic feature of more advanced illness is a very elevated white cell count (in excess of 30,000cells/mm³) which can often rise to this level over a matter of hours. Elevated creatine kinase has also been noted.

4. Diagnosis - points to remember

- This syndrome of severe sepsis related to soft tissue inflammation may be difficult to distinguish from other types of injection site infection in its early stages.
- Specific enquiry should be made about the drug user's recent injection practice, as the illness has been strongly associated with intramuscular and subcutaneous injection.
- Ask about other substances mixed with the heroin for injection e.g. other drugs such as cocaine or cutting agents such as citric acid
- All injection sites should be examined for signs of local inflammation.
- If local inflammation is at all unusual in the ways described above, or if the drug user says that this infection is not like others they have experienced, then clinical suspicion should be high that this could be a case.
- The diagnosis should also be considered in patients who present with systemic signs as described above, and unusual local lesions should be sought on examination of collapsed injecting drug users.
- Drug users may appear well until quite late in the illness.

A one-page summary of diagnosis, investigation and management is attached for your convenience in the clinical setting.

A two-page specimen collection protocol designed to optimize microbiological investigation and referral of samples to Reference Laboratories is also attached.

5. Management

Because of the rapidity with which patients can deteriorate with this condition, **prompt treatment is crucial**. In addition to surgical treatment (including exploration, drainage, and/or debridement of any injection site infection) and other general support, antimicrobial therapy should be given according to locally agreed protocols and all other clinical indications, but should include one or more agents known to be active against anaerobes. For *Clostridium* spp these include **penicillin, metronidazole, and clindamycin**, possibly in combinations. Clindamycin may have some specific advantages in these cases, but it should not be given alone as resistance to this antibiotic has been described.

- Drug users with extensive swelling, pain, oedema, or erythema, and/or central blackening/blistering, at an injection site, should be immediately admitted to hospital for senior surgical consideration of urgent surgical intervention, high dose – **preferably intravenous** – antibiotic therapy, microbiological sampling, close observation in a high dependency unit and general support.
- Early surgical intervention should also be considered for less severe, but still suspicious local lesions, together with microbiological sampling and antimicrobial treatment. If such patients are not admitted, antimicrobial therapy should be given according to locally agreed protocols and other clinical indications, but should include maximal doses of one or more agents known to be active against clostridia following oral administration. These include **amoxicillin, co-amoxiclav, metronidazole, and clindamycin**. For possible cases treated as outpatients, any apparent inflammatory process at an injection site should be examined **daily** until it has subsided.

A short fact sheet has been prepared (attached) which contains advice for drug users who inject heroin to try to prevent them developing the condition. You might like to give this sheet to drug users with whom you have contact.

6. Reporting

Any case of local inflammation in a drug user with features consistent with the description given above, and who has died or been sufficiently unwell to require admission to hospital should be reported to the consultant in communicable disease control at the local health protection unit. It is also important that isolates from IDU's are referred for identification to the appropriate reference laboratory.

References:

Anonymous. Severe unexplained illness among drug injectors: update 5th June 2000. *SCIEH Weekly Report* 2000; **34**: 125.

Greater Glasgow Health Board, SCIEH. Serious unexplained illness among injecting drug users in Scotland and the Republic of Ireland – update. *Eurosurveillance Weekly* 2000; **4**: 000608. (<http://www.eurosurv.org/2000/000608.htm>).

CDSC. Serious unexplained illness among drug injectors. *Commun Dis Rep CDR Wkly* 2000; **10**: 203, 206.

Ahmed S, Gruer L, McGuigan C, Penrice G, Roberts K, Hood J, et al. Unexplained illness and death among injecting-drug users – Glasgow, Scotland; Dublin, Ireland; and England, April-June 2000. *MMWR* 2000; **49**: 489-492.

Andraghetti R., Goldberg D., Smith A., O’Flanagan D., Lieftucht A., Gill N. Severe systemic sepsis associated with soft tissue inflammation in injecting drug users in Scotland, Ireland, England and Wales. *Eurosurveillance Weekly* 2000;31:000803 (<http://www.eurosurv.org/2000/000803.htm>)

Fischer M, Whitney A, Ahmed S, Barry J, and Jones J. Unexplained severe illness and death among injecting drug users in Scotland, Ireland and England from April to August 2000. *Emerging infections* 6, 2004. Chapter 9.

Brazier JS, Gal M, Hall V, Morris TE. Outbreak of *Clostridium histolyticum* infections in injecting drug users in England and Scotland. *Eurosurveillance*, 2004;9(3) 15-16.

Summary- Advice for doctors on diagnosis, management and reporting of severe systemic sepsis related to soft tissue inflammation in injecting drug users

Local signs

Local inflammation at a subcutaneous/intramuscular injection site. Variable features including: oedema (often extensive), myositis, erythema, cellulitis, bruised appearance, abscess-like (with little/no pus), blackened/blistered centre, necrosis, necrotising fasciitis

usually painful

- characteristically not associated with high fever
- may be difficult to distinguish from other types of soft tissue inflammation in its early stages
- ask about injecting practices and about substances co-injected with heroin
- examine all injection sites for signs of local inflammation

Systemic signs

several days after development of local lesion

dramatic deterioration

circulatory collapse &/or ARDS &/or DIC

WCC >30,000 cells/mm³

often remain mentally alert until late stage

- look for unusual local lesions in collapsed injecting drug users

Management

prompt treatment crucial

consider early surgical treatment (exploration, drainage, debridement)

antimicrobials according to local protocol and other clinical indications but including agents active against clostridia

Severe cases should be admitted for consideration of surgical treatment, IV antibiotics (**one/combination of penicillin, metronidazole, clindamycin (not alone)**), microbiological investigation and close observation in a high dependency unit

Cases treated as outpatients should also be considered for surgical intervention, have microbiological sampling and receive antibiotics active against anaerobes when given orally (**amoxicillin, co-amoxiclav, metronidazole, and clindamycin (not alone)**). Any inflammation at an injection site should be examined daily until it has subsided.

Microbiological investigation

Please collect the following specimens for culture in order of priority and transport to your local laboratory as quickly as possible. Please notify the hospital microbiologist that you have a suspect case.

biopsy tissues from local inflammatory lesions

pus/swab of local lesion(s)

blood cultures - at least 2 sets

Any other relevant samples

Reporting

Please report any case with the described features who has died or been sufficiently unwell to be admitted to hospital to your local consultant in communicable disease control

**Specimen Collection Protocol For Clinicians For Microbiological
Investigation of Severe Systemic Sepsis related to Soft Tissue
Inflammation Amongst Injection Drug Users,
England & Wales - July 2008**

The following is a guide for clinicians when taking specimens from *potential* case-patients. In addition to examination in your own laboratory, it is possible that these specimens may be sent to various specialist laboratories for further microbiological and toxicological analysis.

If possible specimens should be collected and transported to a clinical microbiology laboratory as rapidly as possible for testing, and storage. As there is evidence that anaerobic organisms are possibly involved in the aetiology of these cases, speed and maximum efforts to maintain anaerobic conditions in transport of specimens are important. Optimal recovery of fastidious anaerobes is best achieved if samples are processed as soon as possible e.g. within one hour of collection and if exposure to oxygen is kept to a minimum. The experiences of the microbiology investigation team involved in the *C. novyi* outbreak was published by Brazier et al (2002)¹. This report contains advice on optimal isolation and identification of clostridia from IDU's. It may be appropriate to arrange for urgent transportation of the specimen(s) to the microbiology laboratory and immediate processing, if a delay is otherwise anticipated.

Please collect the following specimens in order of **priority** together with any other specimen as clinically indicated. (Please note that though tissue biopsy samples are the most useful, blood cultures and pus/swabs should be collected as soon as possible after admission)

- 1. Biopsy tissues** collected aseptically from local inflammatory lesion, necrosis or abscess, **if surgical debridement is performed:**
 - several samples if possible, quantity is important;
 - tissue placed in sterile containers for direct culture (aerobic and anaerobic) and freezing; and
 - formalin-fixed (10% buffered formalin) or paraffin embedded for histology.

- 2. Pus or swab of local lesion:**
 - pus, as large a volume as feasible, placed in sterile containers for microscopy;
 - aerobic and anaerobic culture; and
 - if no pus available, swab of lesion put immediately into transport media for aerobic and anaerobic culture.

¹ Brazier JS, Duerden BI, Hall V, Salmon JE, Hood J, Brett MM, McLauchlin J, George RC. Isolation and identification of *Clostridium spp.* from infections associated with the injection of drugs: experiences of a microbiological investigation team. *Journal of Medical Microbiology* 2002;51:985-989.

3. Blood cultures:

- ideally at least 2 sets of blood cultures, with at least 1 set prior to antibiotic administration.

4. Serum:

- for local investigations and retention (for possible further testing as appropriate); but NOTE

IF the clinical picture is suggestive of wound **botulism** a serum sample should be forwarded as soon as possible to the HPA, Food Safety Microbiology Laboratory (tel 020 82004400) for the appropriate toxin assay to be performed.

5. Other Body fluids:

- if other, normally sterile, fluid specimens are taken as part of the clinical workup, please ask laboratory to retain the samples rather than discarding after standard testing.

Labelling of samples

Please ensure clear labelling of samples and request forms and note that special investigations and prolonged storage may be required.

If suspected cases are identified please notify the local hospital microbiologist

regarding time, date and nature of sample collected and for further discussion if required.

Isolates from the above specimens suspected of being clostridia should be referred for identification to: Anaerobe Reference Laboratory, NPHS Microbiology Cardiff, University Hospital of Wales, Cardiff, CF14 4XW, marked for the attention of Dr. J.S. Brazier.

If the case is sufficiently unwell to warrant admission to hospital please notify the consultant in communicable disease control

at the local **Health Protection Unit** regarding details of the case. Local officials will then relay information to the Centre for Infections.

Non-cases.

For patients who do not meet all the requirements of a potential case but in whom microbiological testing is felt appropriate a similar investigational approach, in addition to any other clinically indicated investigations, may be helpful.