Interim Clinical Guidance for the Management of Suspected Anthrax in Drug Users

This guidance applies to cases of suspected anthrax in heroin users and is based on that used during the 2009/10 outbreak in Scotland.

The guidance supplements the clinical algorithm (Figure 1) which provides a quick guide to key diagnostic features and management.

This guidance is intended to assist clinicians in the management of patients with suspected or confirmed systemic anthrax infection under their care. It provides information on clinical assessment of anthrax infection and best available advice on management, derived from current experience in managing cases.

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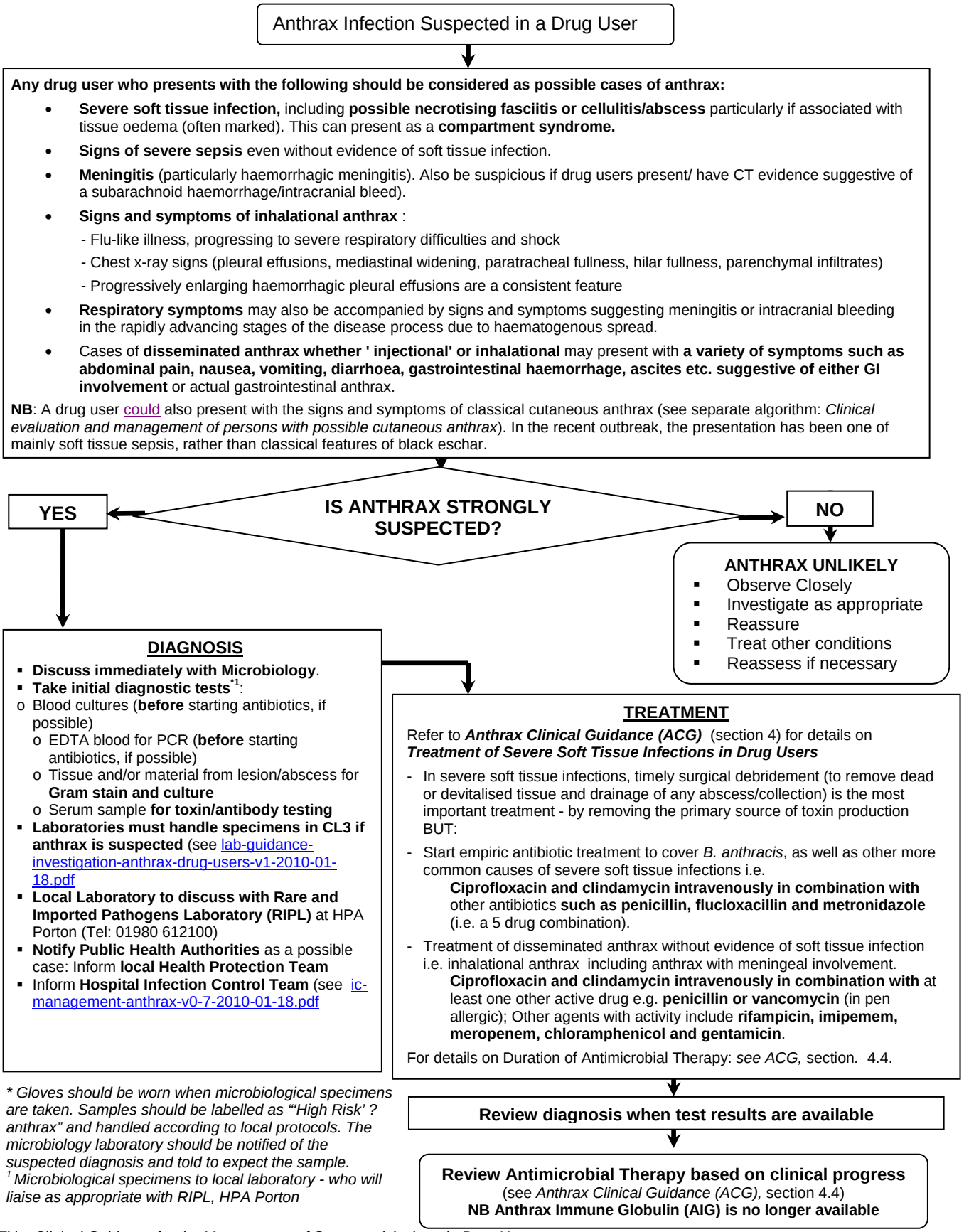
1. Suspected Anthrax Cases Recommendations for Clinical Management — Summary

(See also Clinical Algorithm (Figure 1) for more details)

- **Immediate treatment** must include:
    - **Appropriate antimicrobial therapy, after taking appropriate specimens**, particularly blood cultures, EDTA for PCR and serum for toxin levels/serology;
    - Where there is skin and soft tissue involvement - urgent **Surgical consultation / debridement**.
- **Urgent discussion** is advised with the **Local Microbiology Department**:
    - with respect to appropriate diagnostic specimens, infection control issues and antimicrobial treatment**;**
- **Also contact at an early stage**:
    - **The local ITU** should be informed because of the potential for acute deterioration.
    - Further management advice may be sought from the **local Infectious Diseases (ID) Physicians**.
    - **The local Infection Control Team** should be advised of a possible case.
    - The local **Health Protection Team** (Public Health) should be notified (anthrax is a notifiable disease[1]).

[1] Part 2 (Notifiable Diseases, Organisms and Health Risk States) of the Public Health etc.(Scotland) Act came into effect on 1 January 2010. http://www.scotland.gov.uk/Resource/0039/00398230.doc

Figure 1. *Clinical Algorithm. Clinical Evaluation and Management of Drug Users with Possible Anthrax*



2. Clinical diagnosis

Anthrax infection should be considered in **drug users** particularly **heroin users**, especially those who inject intramuscularly, intravenously, or who take heroin by any other route (smoking or snorting) who present with (see also table 1):

- **Cellulitis / soft tissue infection**, especially if associated with **significant oedema**, with or without systemic illness;

- Other presentations including:

    - **gastrointestinal (GI) symptoms** (abdominal pain, GI bleeding, nausea, vomiting, diarrhoea)

    - **CNS related symptoms** (resembling meningitis or subarachnoid haemorrhage or CT evidence of subarachnoid haemorrhage/intracranial bleed);

    - or less commonly **respiratory signs and symptoms** may occur (see clinical algorithm and Table 1 for the symptoms and signs of inhalational anthrax).

- **"Classical" cutaneous** anthrax (black eschar lesions) was **not** a presentation seen in the 2009/10 outbreak but could still occur.

The following patterns of **clinical presentation and progression** are emerging as important:

- Marked muscle and soft tissue involvement **that does respond** to appropriate debridement and antimicrobial therapy.

- **Severe muscle and soft tissue involvement** that despite optimal surgical debridement / antimicrobial therapy / ITU support still has a high mortality. The predictors of mortality in this group are not clear.

- A **meningo-encephalitic / meningitic presentation** with associated septic markers which on CT shows evidence of intracranial bleeding suggestive of subarachnoid haemorrhage. These cases have progressed rapidly to death.

- **Abdominal pain** and **gastrointestinal symptoms** suggesting GI involvement.

The different presentations may be present individually or together, and vary in severity depending on the mode of infection; "skin / muscle popping", direct IV injection or inhalation / "snorting", although there is no clear relationship with the route of taking heroin to date.

Obtaining initial laboratory evidence of infection is very important in making the diagnosis of anthrax.

Table 1: Clinical features of Anthrax in Drug Users in Scotland[2]			
Case Presentation	**Clinical appearance**	**Clinical progression**	**Investigations**
Skin and soft tissue infection	- The appearances are variable but oedema is prominent. **Oedema** is usually significant and in excess of the area of induration. Oedema may spread over a wide area. (See table 2). - Abnormality is usually seen around the injection site. - In some cases **erythema** and **induration** is minimal. - NB. **Black eschar** and **necrosis** as seen in typical cutaneous anthrax has not been seen to date in the present outbreak but could occur.	- Patients may present at a variety of stages and have a variable course. - **Systemic** features are **non specific**. - **Temperature** is usually normal. - Patients may appear **very unwell** with peripheral shut down despite normal BP, respiratory rate and oxygenation. - **Tachycardia** is common. - **Fluid requirements** are often very high in excess of 10l/24hours. Fluid may collect as **ascites** +/- **pleural effusions**. - A **biphasic illness** has been noticed with initial response to therapy followed by a sudden and rapid decline in physiology.	- Results are variable. Of note the WCC, CRP, lactate, H+ and CK are often normal. - A **decline in platelet count** seems to herald a clinical decline. - **Coagulopathy** can develop and **bleeding** can become significant around the debridement site. - **Renal impairment** can initially respond to fluid resuscitation but can progress despite this.
CNS: Meningo-encephalitis / haemorrhagic meningitis / possible subarachnoid haemorrhage	- Neurological presentation has been with severe agitation described as "**thrashing**", and reduced GCS. - **Seizures** may occur. - There may be signs of skin and soft tissue infection, but equally these may not be present. - A clear history of drug use or signs of injecting should be looked for.	- CT scans show intracranial **blood** and features of a **subarachnoid haemorrhage**. - There has been a **rapid decline in GCS** with **subsequent shock**, and **mortality** has been 100%.	- CT Scan shows **intracranial haemorrhage**. - **Blood cultures may be positive** for anthrax.

[2] This reflects the experience of a small number of cases that were seen in Scotland from December 2009 to March 2010. Common features have been highlighted. Not all features listed below are seen and other symptoms and signs can occur. This is not a definitive list.

Table 1 (continuation)	
Case Presentation	**Clinical appearance**
Gastrointestinal symptoms / GI anthrax	- GI anthrax has not been definitively seen although some patients with anthrax have had **GI signs and symptoms**, e.g. **abdominal pain, nausea, vomiting, (diarrhoea), ascites, GI haemorrhage**. These features may simply be present as evidence of disseminated disease.
Inhalational anthrax / respiratory	- Some anthrax patients in this outbreak with systemic illness have developed **pleural effusions**. - Inhalation of contaminated heroin remains a possible explanation in some cases. However, full classical inhalation anthrax has not yet occurred. - Classically, the presentation of inhalation anthrax is with a flu-like illness with a biphasic course **progressing rapidly to toxaemia and death**. **Drenching sweats** were also a common feature of the cases of inhalational anthrax cases (US, 2001[3]). - In addition to classically progressive and haemorrhagic pleural effusions a **widened mediastinum** may be seen on chest X-ray or chest CT. A large proportion of inhalational cases may also develop CNS symptoms with a haemorrhagic meningitis. - **Atypical inhalation anthrax** may also occur (without classical X-ray changes) presenting as systemic illness. - It is theoretically possible that any of these presentations could occur in those people that inhale drugs contaminated with anthrax spores.
Cutaneous anthrax	- The classical presentation of cutaneous anthrax, normally due to spores entering the skin via cuts / abrasions, has not been seen yet in this outbreak. - Classically, **cutaneous anthrax** is often a **relatively mild superficial infection** with induration, lack of pain, itch and black scar formation. This is not the presentation seen in injecting drug users to date - who are injecting the spores into a deeper area and are consequently more likely to go on to have a severe local and systemic infection, as described above. - However, the classical picture of a **painless black eschar** may still occur.

[3] Jernigan JA, Stephens DS, Ashford DA *et al* (2001) Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerging Infectious Diseases* **7**, (6): 933-944

3. Differential Diagnosis

The differential diagnosis must include other Severe Skin and Soft Tissue Infection (SSTI) e.g. abscess formation, cellulitis, necrotising fasciitis and streptococcal toxic shock syndrome. Rarely other pathogens seen in Drug Users (DU) can cause significant oedema e.g. *Clostridium novyi*. Table 2 helps to distinguish anthrax from other important aetiologies in this patient group.

Table 2: Differentiation of Severe Soft Tissue Infection (SSTI) in Drug Users (DU)

Diagnostic Feature	Abscess	Cellulitis	Necrotising Fasciitis	Anthrax with severe soft tissue involvement
Skin and Soft Tissue Appearance	Localised swelling + skin reaction, fluctuance	Extensive hyperaemic erythema, hot	Dusky looking. May be initially fairly normal. Reduced capillary refill in more central areas of erythema; fixed staining / purpura / patchy necrosis	May be little erythema or necrosis. Patches of confluent necrosis, with rim of hyperaemic cellulitis, florid oedema
Systemic Condition	Mild - moderate reaction	Marked reaction, but proportionate to skin findings	Marked reaction which is disproportionately severe compared to the degree of skin / soft tissue involvement	Minimal reaction which is disproportionately mild compared to the degree of skin / soft tissue involvement
Oedema / induration	Minimal	Moderate, but largely confined within area of erythema	Moderate	Very florid locally & may extend very distant to zone of skin change
CRP	CRP mild - moderate elevation	CRP moderate elevation	CRP moderate elevation (disproportionately high for skin change)	CRP may be normal / minimally elevated (disproportionately low for skin change)
Renal Function	Usually normal	Mild – moderate dysfunction	Normal / moderate / severe dysfunction	May be initially good or respond to fluid challenge then profound, pre-terminal rise in creatinine
Haematology	WCC mildly elevated, Hb/Plt unaffected	WCC mild - moderately elevated, Hb/Plt unaffected	WCC moderate-severely elevated, Hb mild - moderate reduction, Plt mild - moderate reduced	May be no increase in WCC initially but can be elevated. With clinical progression Hb & Plt can reduce.
Pain	Mild - moderate	Mild - moderate	Severe pain in excess of clinical appearance is seen at first	No or minimal pain initially. This can worsen and eventually be severe
Temperature	Mildly elevated	Moderate - severe elevation	Moderate elevation / reduced core temperature	Largely normal

4. Case Management of Anthrax in Drug Users (DU), including Severe Soft Tissue Infections (SSTI)

4.1. Immediate management

- Appropriate fluid resuscitation and management of shock. Patients may need large volumes of IV fluids.
- **Most importantly,** if at all possible**, take blood cultures and EDTA for PCR <u>before</u> the administration of any antimicrobials** (as one dose (in anthrax) may be sufficient to sterilise the blood). Also take clotted blood sample for toxin/serology.
- Appropriate blood tests, including FBC, CRP, U/E, CK, lactate, coagulation screen, Group and Save (at least 4 units of blood).
- Contact **Microbiology** for advice on diagnostic tests, infection control and on appropriate antimicrobial treatment (as per clinical algorithm, Figure 1). For duration of antimicrobial therapy, see section 4.4.
- Contact **Surgeons (if SSTI related)** as soon as possible.
- **Urgent Gram stain** of tissue, pus or body fluids (when available).
- Inform: local **Health Protection Team (Public Health), ITU, ID Physicians and Infection Control** (Figure 1).

4.2. Surgical management (if SSTI)

Continued presence of bacilli within a focus of necrotic / under-perfused tissue is to be regarded as incurring 100% mortality.

- An urgent surgical review is indicated (as with necrotising fasciitis) Discuss with Plastic Surgery services if there is any uncertainty over management.
- Arrange blood products as directed by platelet and coagulation results.
- Surgical excision of small necrotic areas may be required for diagnostic purposes. This should be done urgently and as part of surgical exploration unless patient is systemically normal.
- Imaging should not delay urgent debridement of necrotic tissue.

- Exploratory surgery:

    1. Theatre staff to be informed of potential diagnosis, to permit “high risk case” procedures to be instigated (see local Infection Control Guidelines). Note: high concordance with Hep C infection.

    2. Use coagulation diathermy in view of established / impending coagulopathy, with smoke evacuation system. Consider use of tourniquet.

    3. Initial tissue biopsy to be sent at start of procedure for culture & **urgent Gram Stain** (clearly marked as suspected anthrax case & discussed with on-call microbiologist).

    4. Subsequent excision of affected skin with >2cm margin, and any further areas that show alteration in character of the sub-dermal fat. Excise to fascia will facilitate haemostasis.

    5. Widely excise any needle track from within muscle.

    6. Intra-operatively, affected tissue may appear grossly normal. There may not be the clear distinction between healthy and affected tissue unlike in necrotising fasciitis (see table 2). Plane of oedema & fat necrosis is principally sub-dermal, not suprafascial as in necrotising fasciitis. Fasciolysis & microvascular thrombosis markedly less evident than necrotising faciitis. Small vessel bleeding & blood loss more dramatic than in fasciitis & not self-limiting as in severe cellulitis.

    7. Use irrigation. Consider use adrenaline soaks (1:250,000 in saline) prior to revising haemostasis.

    8. Compartment syndrome has been noted in some cases and decompressing incisions may be required. These may also serve to enhance tissue perfusion, and so antibiotic delivery, in the face of rapidly developing oedema.

    9. Apply *Surgicel* ® as first layer of wound dressing in view of established / incipient coagulopathy, followed by non-adherent layer, and bulky gauze / occlusive layer / wool & crepe pressure dressing.

    10. Local excision of any distant lesions exhibiting any fluctuance / induration / oedema / necrosis / erythema. Review body surface for such lesions prior to recovering patient & exiting theatre.

    11. Insert finebore nasogastric feeding tube. ITU care post-op.

- Delay reconstruction until coagulopathy is corrected and nutritional parameters adequate. Consider temporising use of vacuum assisted dressings.

- Review need for further debridement at 12 & 24 hours, thereafter minimum of daily. Observe for skin changes & worsening oedema.

4.3. Supportive and further management

- A proportion of patients will require ITU management initially and where an outreach service is provided they should be reviewed daily if on a general ward.

- The patient may appear well and then have a rapid decline to shock over a very short period of time. The patient will usually feel unwell and may appear clinically shut down but with normal BP. Tachycardia is usually present.

- BP, WCC, lactate, H+ and CRP may be disproportionately normal or near normal. and do not correspond to the severity of the illness.

- Fluid requirements may be very high.

- Bloods including coagulation, FBC and renal function should be measured ideally twice daily. Bleeding may be out of proportion to the degree of coagulopathy on laboratory testing.

- A drop in platelets may be the first parameter that heralds a rapid progression to shock and this should be discussed with ITU.

- Any clinical decline, drop in platelets or Hb, worsening coagulation or renal function requires urgent discussion with senior staff and ITU.

- Pleural or ascitic fluid contains toxin and must be drained usually with an indwelling catheter as fluid will recur.

4.4. Duration of Antimicrobial Therapy

In the 2009/10 outbreak of anthrax in injecting drug users, in our experience patients who have survived severe/systemic illness have been on appropriate antimicrobials for 3 to 4 weeks, initially IV (with 3 agents) and latterly orally with ciprofloxacin and clindamycin.

However, we suggest that after 10-14 days therapy, antimicrobial treatment should be reviewed and either continued, the regimen modified with regard to choice of agent and route of administration, or stopped depending on the clinical course of the individual patient. When antimicrobial therapy is stopped patients must be monitored for the worsening of symptoms and if discharged should be educated in the need to return to hospital for review if symptoms recur. Antimicrobials should be re-started if clinically appropriate but as there may be a remaining focus of infection further surgical debridement must also be considered.

This recommendation essentially follows the WHO, 2008 guideline in cases of systemic anthrax or life threatening disease which suggests a minimum of 10-14 days therapy with three agents – namely ciprofloxacin (IV at first) with at least 1 more additional agent with adequate CNS penetration (ampicillin or penicillin, meropenem, rifampicin or vancomycin[4]). The rationale for this approach is given by Stern *et al* (2008) who argue that the evidence suggests that meningeal / CNS involvement should be suspected in all cases of systemic anthrax / severe disease. We also include clindamycin in the regimen on the basis that it inhibits protein synthesis and consequently may reduce toxin production, and together with ciprofloxacin has good tissue penetration.

The concept of prolonged antimicrobial treatment in anthrax is based on animal models (delayed germination) and the experience in Russia with a prolonged incubation period observed in some of the inhalational cases in Sverdlovsk in 1979[5], and on the prolonged course of treatment and time to recovery for successfully treated inhalation anthrax cases from 2001 and 2006.

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[4] The duration of therapy suggested by WHO, 2008 (in Anthrax in Humans & Animals, 4th Edition Chapter 7, page 82) for cases of systemic anthrax is 10-14 days. CDC, in the Conference report on Public Health and Clinical Guidelines for Anthrax, 2008 (Stern EJ, Uhde KB, Shadomy SV, Messonnier N. Conference report on public health and clinical guidelines for anthrax [conference summary]. *Emerg Infect Dis* [serial on the Internet]. 2008 Apr [*date cited*]. Available from http://www.cdc.gov/EID/content/14/4/e1.htm) stated 'Participants recommended continuing the current 60-day course of antimicrobial therapy, with adjustment of the regimen based on the clinical course of the disease in patients' for cases of inhalation anthrax and serious systemic illness from anthrax.

[5] Wilkening, DA. (2006) Sverdlovsk revisited: Modeling human inhalation anthrax. *PNAS* **103,** (20): 7589-7594.

Meselson M, Guillemin J, Hugh-Jones M, Langmuir A, Popova I, Shelokov A, et al. The Sverdlovsk anthrax outbreak of 1979. *Science* 1994; 266:1202–8

Notes

Note that in the terminal stages of disseminated anthrax (occurring from any route of infection) the patient is likely to be coagulopathic and may present with external bleeding from orifices. In such terminal cases, if untreated with antimicrobials, the blood will contain large numbers of vegetative organisms. **Such cases will present the highest infection control risk** (refer to the Anthrax Outbreak Infection Control Guidelines*).

Cases that have occurred among drug users since December 2009 have shown a number of clinical features that may help to distinguish anthrax from other more common forms / aetiologies of cellulitis / severe soft tissue infections (including necrotising fasciitis) in injecting drug users (see *Interim Clinical Guidance,* table 2). **Please note that *B.anthracis* may not be the sole pathogen and *Staph. aureus, Group A Streptococci* and anaerobes etc may also be involved.**

* http://www.documents.hps.scot.nhs.uk/giz/anthrax-outbreak/ic-management-anthrax-v0-7-2010-01-18.pdf

5. Pathology of Anthrax

Anthrax is caused by infection with the spores of *Bacillus anthracis*, a naturally occurring organism found over most of the world. The disease primarily affects herbivores, which ingest the spores in water or when feeding from contaminated ground and develop a severe systemic infection.

The spores germinate and as vegetative bacteria spread through the animal's body reaching very high levels (around 10^8/ml). The infection interferes with normal blood clotting and around the time of death the animal bleeds profusely and the contaminated body fluids spill onto the soil. In contact with air and soil, the bacteria form spores, which are the infectious form. Spores are extremely resistant and can persist in the environment and on animal products, especially skins for many decades.

Human infection occurs by contact with spores by one of several routes, which lead on to a characteristic disease:

1. ***Injection anthrax*** has occurred in injecting drug users and has a variety of presentations, ranging from a necrotising fasciitis like syndrome or cellulitis with marked oedema, through to rapid septicaemic illness and death.

2. ***Anthrax meningitis*** may be the main presenting sign or one of several signs in any form of disseminated/septicaemic anthrax

3. **Cutaneous anthrax** occurs when spores enter through an abrasion in the skin. This is the commonest natural form of anthrax but has not featured in the current outbreak among drug users. There is a local lesion, characterised by a skin lesion which expands to give an obvious soft tissue infection with considerable oedema. The lesion ulcerates, and then develops a black eschar, slowly resolving with the oedema subsiding and the lesion healing. In 10% or so of cases, systemic anthrax develops with sever septicaemia and death.

4. ***Gastro-intestinal anthrax*** follows the ingestion of anthrax spores (e.g. consumption of contaminated meat or via snorting contaminated drugs). The disease affects the gut with widespread haemorrhage and septicaemia usually leading to death.

5. ***Inhalational anthrax*** is acquired by inhalation of spores, usually from handling contaminated animal skins or wool (but potentially form smoking contaminated drugs) and is the rarest natural form. The disease is essentially a mediastinitis with septicaemia, leading to ARDS and pleural and pericardial effusions.

Whatever the portal of entry, anthrax spores are taken up by macrophages and germinate to produce the vegetative bacteria, which appear in the tissue and lymph nodes. These bacteria rapidly reproduce by binary fission, and elaborate the toxin which has three parts, Protective Antigen (PA), Lethal Factor (LF) and Oedema Factor (EF). PA molecules are activated at the surface of host cells and combine to form a heptamer which acts as the conduit for either EF or LF to enter the cell. EF affects the cell water balance through the cyclic AMP system and results in the tissue oedema. LF is lethal for macrophages and so effectively inactivates one of the major phagocytic and immune coordinating cells of the host's defence system.

The bacilli also form a protective capsule which makes them resistant to phagocytosis by other cells. Once the number of bacteria reach a critical level they spill into the circulation,

and aided by the toxin which eliminates an effective immune response reproduce rapidly. The combined effects of the dysfunctional immune system (primarily the non-specific response) and the tissue damage from the toxin cause activation of the coagulation, complement and inflammatory pathways. There is massive leakage of fluid from the vascular compartment, giving pulmonary effusion and ARDS, with systemic shock and a consumptive coagulopathy with disseminated intravascular coagulation, a marked fall in platelets and bleeding.

Death results from the multi-organ damage, shock and hypoxia and there may be significant bleeding from orifices before and after death. The bacteraemia is exceptionally high, reaching 10^8/ml. In cutaneous anthrax which does not lead to a systemic infection, antibodies against PA and LF appear as the patient recovers and the lesion subsides.