

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

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*This guidance applies to cases of suspected anthrax in drug heroin users during the current outbreak in Scotland<sup>1</sup>. It will be modified as further information indicates that adjustments in approach to control and management are appropriate.*

*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.*

*Advice is also provided on the use of anthrax immune globulin (AIGIV) and how to obtain it in Scotland. (For the rest of the UK, please contact your local Health Protection Unit or service provider, e.g. HPA or equivalent.)*

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<sup>1</sup> CMO Letter. *Outbreak of Anthrax Infections in Heroin Drug Users*. (22<sup>nd</sup> Jan 2010) Available at <http://www.hps.scot.nhs.uk/anthrax/documents/cmo-letter-anthrax-2010-01-22.pdf>

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# 1. Suspected Anthrax Cases Recommendations for Clinical Management

## Summary

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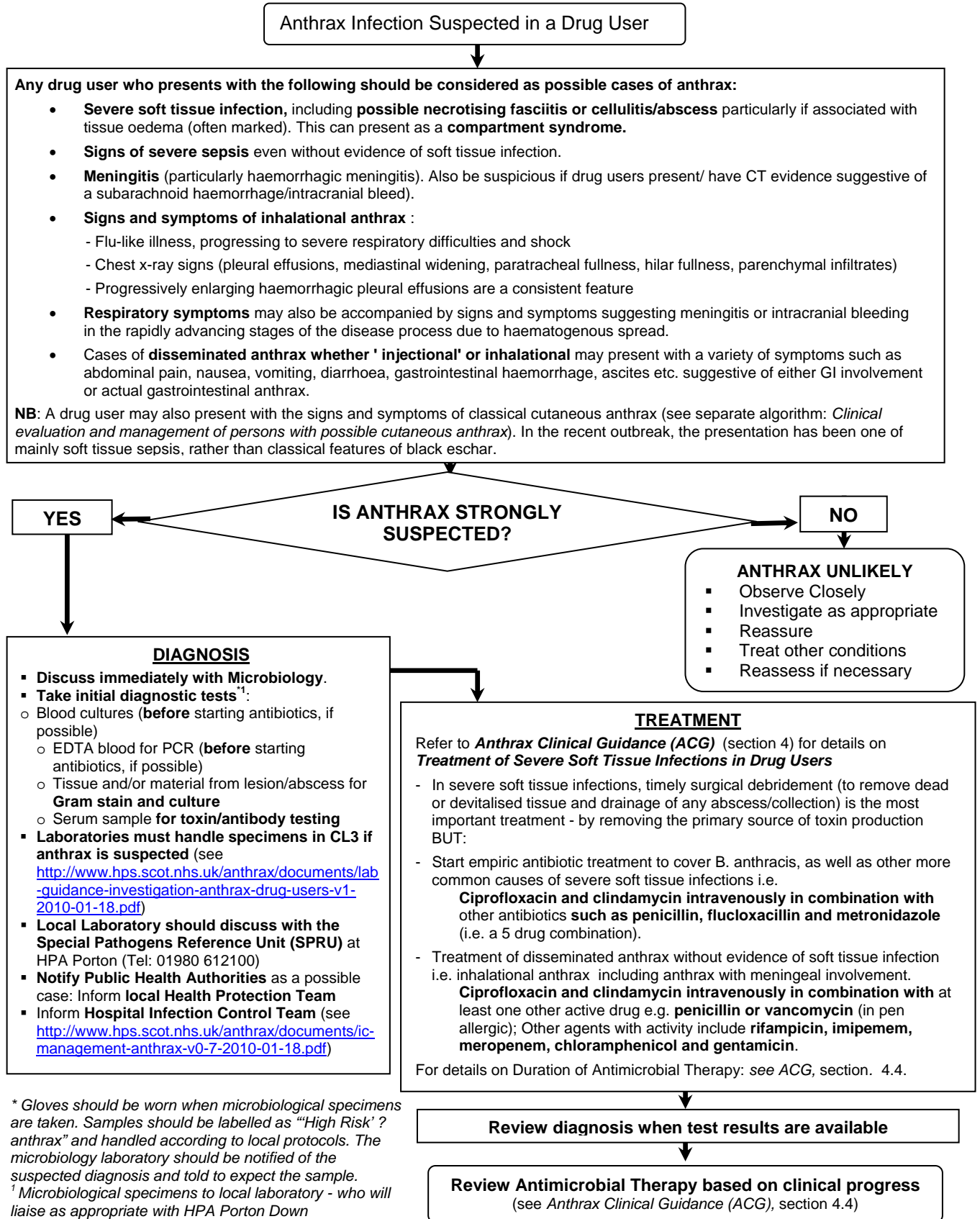
(See also Clinical Algorithm (Figure 1) for more details)

- **Immediate treatment** must include:
  - o **Appropriate antimicrobial therapy, after taking appropriate specimens**, particularly blood cultures, EDTA for PCR and serum for toxin levels/serology;
  - o Where there is skin and soft tissue involvement - urgent **Surgical consultation / debridement**.
- **Urgent discussion** is advised with the **Local Microbiology Department**:
  - o with respect to appropriate diagnostic specimens, infection control issues and antimicrobial treatment;
- **Also contact at an early stage**:
  - o **The local ITU** should be informed because of the potential for acute deterioration.
  - o Further management advice may be sought from the **local Infectious Diseases (ID) Physicians**.
  - o **The local Infection Control Team** should be advised of a possible case.
  - o The local **Health Protection Team** (Public Health) should be notified (anthrax is a notifiable disease<sup>2</sup>).
- **Post first line treatment**
  - o **Anthrax antitoxin (Anthrax Immune Globulin Intravenous (Human) (AIGIV))** may be of additional benefit and should be considered (see appendix 1).

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<sup>2</sup> Part 2 (Notifiable Diseases, Organisms and Health Risk States) of the Public Health etc.(Scotland) Act came into effect on 1 January 2010. See Scottish Government guidance on the new notification requirements at: <http://www.scotland.gov.uk/Topics/Health/NHS-Scotland/publicact/Implementation/Timetable3333/Part2Guidance/Q/EditMode/on/ForceUpdate/on>

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



\* *Gloves should be worn when microbiological specimens are taken. Samples should be labelled as "High Risk" ? anthrax" and handled according to local protocols. The microbiology laboratory should be notified of the suspected diagnosis and told to expect the sample.*

<sup>1</sup> *Microbiological specimens to local laboratory - who will liaise as appropriate with HPA Porton Down*

## 2. Clinical diagnosis

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**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:
  - o **gastrointestinal (GI) symptoms** (abdominal pain, GI bleeding, nausea, vomiting, diarrhoea);
  - o **CNS related symptoms** (resembling meningitis or subarachnoid haemorrhage);
  - o or less commonly **respiratory signs and symptoms** may occur.
- **“Classical” cutaneous anthrax** (black eschar lesions) has **not** been a presentation seen in the current 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<sup>3</sup>**

Case Presentation	Clinical appearance	Clinical progression	Investigations
<b>Skin and soft tissue infection</b>	<ul style="list-style-type: none"> <li>- The appearances are variable but oedema is prominent. <b>Oedema</b> is usually significant and in excess of the area of induration. Oedema may spread over a wide area. (See table 2).</li> <li>- Abnormality is usually seen around the injection site.</li> <li>- In some cases <b>erythema</b> and <b>induration</b> is minimal.</li> <li>- NB. <b>Black eschar</b> and <b>necrosis</b> as seen in typical cutaneous anthrax has not been seen to date in the present outbreak but could occur.</li> </ul>	<ul style="list-style-type: none"> <li>- Patients may present at a variety of stages and have a variable course.</li> <li>- <b>Systemic</b> features are <b>non specific</b>.</li> <li>- <b>Temperature</b> is usually normal.</li> <li>- Patients may appear <b>very unwell</b> with peripheral shut down despite normal BP, respiratory rate and oxygenation.</li> <li>- <b>Tachycardia</b> is common.</li> <li>- <b>Fluid requirements</b> are often very high in excess of 10l/24hours. Fluid may collect as <b>ascites +/- pleural effusions</b>.</li> <li>- A <b>biphasic illness</b> has been noticed with initial response to therapy followed by a sudden and rapid decline in physiology.</li> </ul>	<ul style="list-style-type: none"> <li>- Results are variable. Of note the WCC, CRP, lactate, H+ and CK are often normal.</li> <li>- A <b>decline in platelet count</b> seems to herald a clinical decline.</li> <li>- <b>Coagulopathy</b> can develop and <b>bleeding</b> can become significant around the debridement site.</li> <li>- <b>Renal impairment</b> can initially respond to fluid resuscitation but can progress despite this.</li> </ul>
<b>CNS: Meningo-encephalitis / haemorrhagic meningitis / possible subarachnoid haemorrhage</b>	<ul style="list-style-type: none"> <li>- Neurological presentation has been with severe agitation described as "<b>thrashing</b>", and reduced GCS.</li> <li>- <b>Seizures</b> may occur.</li> <li>- There may be signs of skin and soft tissue infection, but equally these may not be present.</li> <li>- A clear history of drug use or signs of injecting should be looked for.</li> </ul>	<ul style="list-style-type: none"> <li>- CT scans show intracranial <b>blood</b> and features of a <b>subarachnoid haemorrhage</b>.</li> <li>- There has been a <b>rapid decline in GCS</b> with <b>subsequent shock</b>, and <b>mortality</b> has been 100%.</li> </ul>	<ul style="list-style-type: none"> <li>- CT Scan shows <b>intracranial haemorrhage</b>.</li> <li>- <b>Blood cultures may be positive</b> for anthrax.</li> </ul>

<sup>3</sup> This reflects the experience of a small number of cases that have been 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
<b>Gastrointestinal symptoms / GI anthrax</b>	<ul style="list-style-type: none"> <li>- GI anthrax has not been definitively seen although some patients with anthrax have had <b>GI signs and symptoms</b>, e.g. <b>abdominal pain, nausea, vomiting, (diarrhoea), ascites, GI haemorrhage</b>. These features may simply be present as evidence of disseminated disease.</li> </ul>
<b>Inhalational anthrax / respiratory</b>	<ul style="list-style-type: none"> <li>- Some anthrax patients in this outbreak with systemic illness have developed <b>pleural effusions</b>.</li> <li>- Inhalation of contaminated heroin remains a possible explanation in some cases. However, full classical inhalation anthrax has not yet occurred.</li> <li>- Classically, the presentation of inhalation anthrax is with a flu-like illness with a biphasic course <b>progressing rapidly to toxemia and death</b>. <b>Drenching sweats</b> were also a common feature of the cases of inhalational anthrax cases (US, 2001<sup>4</sup>).</li> <li>- In addition to classically progressive and haemorrhagic pleural effusions a <b>widened mediastinum</b> 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.</li> <li>- <b>Atypical inhalation anthrax</b> may also occur (without classical X-ray changes) presenting as systemic illness.</li> <li>- It is theoretically possible that any of these presentations could occur in those people that inhale drugs contaminated with anthrax spores.</li> </ul>
<b>Cutaneous anthrax</b>	<ul style="list-style-type: none"> <li>- The classical presentation of cutaneous anthrax, normally due to spores entering the skin via cuts / abrasions, has not been seen yet in this outbreak.</li> <li>- Classically, <b>cutaneous anthrax</b> is often a <b>relatively mild superficial infection</b> 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.</li> <li>- However, the classical picture of a <b>painless black eschar</b> may still occur.</li> </ul>

<sup>4</sup> 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.

<b>Table 2: Differentiation of Severe Soft Tissue Infection (SSTI) in Drug Users (DU)</b>				
<b>Diagnostic Feature</b>	<b>Abscess</b>	<b>Cellulitis</b>	<b>Necrotising Fasciitis</b>	<b>Anthrax with severe soft tissue involvement</b>
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)

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### 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 before 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).
- Consider the **possible use of Anthrax Immunoglobulin IV (AIGIV)** (see section 4.4 and appendix 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 fasciitis. 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**

- Consider Anthrax Immunoglobulin IV (AIGIV) if patient fits clinical definition and is a confirmed case or a probable case where Gram stain identifies suspicious Gram positive bacilli (see appendix 1).
- Most 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.
- 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 present 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<sup>5</sup>). 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<sup>6</sup>, 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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<sup>5</sup> 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.

<sup>6</sup> 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

# Appendix 1

## Guidance on the use of Anthrax Immune Globulin Intravenous (Human) (AIGIV) in Scotland

**First line treatments** for anthrax among drug users must be initiated rapidly and consists of:

- 1) **Appropriate antimicrobial therapy after taking appropriate specimens**, particularly blood cultures, EDTA for PCR and serum for toxin levels / serology;  
PLUS
- 2) **Surgical debridement** of any skin / soft tissue involvement especially in injection users.

**Anthrax Immune Globulin Intravenous (Human) – anthrax antitoxin – maybe of additional benefit in limiting the effect of anthrax toxins, following first line treatment.**

### I. Background

The following guidance is intended to assist clinicians in the process of assessing whether a patient with systemic anthrax infection under their care is likely to benefit from the use of **Anthrax Immune Globulin Intravenous (Human) (AIGIV)**. It provides information on clinical assessment of anthrax infection, the criteria for the use of AIGIV in such patients, and a Q&A on AIGIV.

If the clinical criteria for use of AIGIV have been met, the *HPS Protocol for the Release of AIGIV in Scotland* should be followed (appendix 2). (NB. In the rest of the UK, please contact your Health Protection Unit, HPA or equivalent Health Protection organisation.)

Consider anthrax infection in any drug users, particularly heroin users, especially those who inject intravenously, intramuscularly or by any other injection route, presenting with a systemic illness and cellulitis associated with significant oedema. Other presentations include respiratory symptoms, signs and CXR / CT changes. In disseminated cases, a high proportion may present with CNS signs and symptoms, while others may also have signs indicating gastrointestinal involvement (see previous table 1 of the *Clinical Guidance* for more detailed descriptions of other presentations).

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\*).

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

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.anthraxis* may not be the sole pathogen and *Staph. aureus*, *Group A Streptococci* and anaerobes may also be involved.

## II. Assessment of a Patient for AIGIV use

### 1) Clinical criteria

Patients must meet the following criteria before AIGIV can be considered

- 1) There must be an epidemiological link to a potential anthrax exposure, e.g. a drug (heroin) user

#### AND EITHER

- 2) 2.1. **Systemic illness in a drug user with one or more of the following 5 clinical presentations:**
  - 2.1.1. **Severe cellulitis / soft tissue infection**, especially if accompanied by **substantial soft tissue oedema. This may also present as a compartment syndrome.**

Lack of significant oedema is more consistent with other infectious agents commonly seen in IVDU's.

NB: Clostridium novyi related SSTI in injecting drug users also classically present with significant soft tissue oedema. However, unlike anthrax, this organism is almost never isolated from the blood stream nor often seen in Gram films of tissue.
  - 2.1.2. **Sudden onset of sepsis with no other obvious source.**

Large volume fluid resuscitation is frequently required. Significant peripheral shut-down & tachycardia, with an initially well maintained BP has been seen in a number of cases before rapid irrecoverable shock ensues.
  - 2.1.3. **CNS signs and symptoms suggesting meningitis, or subarachnoid haemorrhage / intracranial bleed.**

A few cases have presented clinically as a subarachnoid haemorrhage with CT scans consistent with this diagnosis. A presentation consistent with bacterial meningitis but with a haemorrhagic CSF has also occurred.
  - 2.1.4. **Respiratory symptoms** – suggesting possible inhalational anthrax or disseminated disease.

If heroin is smoked (or snorted) it is theoretically possible to develop inhalational anthrax, which can present with chest pain, dyspnoea and have chest X-ray findings of progressive (haemorrhagic) pleural effusions (and classically a widened mediastinum). This may also present with a flu-like initial presentation and develop as a biphasic illness. Drenching sweats were also a common feature of the 2001 inhalational cases in the US (Jernigan *et al*, 2001<sup>4</sup>).

Other differential diagnoses commonly seen in this group such as pulmonary thromboembolism and pneumonia should be considered.
  - 2.1.5. **GI symptoms** – suggesting possible gastrointestinal anthrax or evidence of disseminated disease.

A heroin user, especially if snorting heroin, may present with gastrointestinal haemorrhage. However, GI symptoms are commonly seen in patients with disseminated anthrax (Jernigan *et al*, 2001<sup>4</sup>).

#### OR

- 2.2. **A case with features clinically compatible with cutaneous, inhalation, or gastrointestinal anthrax illness with systemic effects** (including malaise, myalgias, or fever).

#### PLUS

- 3) **Either “confirmed” case status:** isolation of *Bacillus anthracis* or other laboratory evidence of anthrax after discussion with a local Microbiologist or the *Special Pathogens Reference Laboratory*, HPA Porton Down.  
**or** **“probable” case status** by visualisation of a Gram positive bacillus consistent with *B. anthracis*, from blood, tissue or a normally sterile site.

## 2) Clinical Assessment for Treatment with AIGIV

AIGIV is intended only as an **adjunctive therapy** and is not intended to be a substitute for first line treatment.

Before the use of AIGIV can be considered, **the patient must have been administered appropriate antimicrobials and have had relevant senior surgical opinion / debridement as required.**

Patients who are potential anthrax cases should be assessed for treatment with AIGIV by the consultant responsible for care as soon as possible in the clinical course as the evidence suggests that treatment is most likely to be effective early in the clinical course, before there is substantial toxin-mediated tissue damage.

AIGIV is supplied by agreement with the US CDC and US FDA on the basis of specific criteria detailed in a CDC E-IND protocol. AIGIV may only be used on a named patient basis by prior agreement with CDC and the US FDA. AIGIV is not licensed for use in the U.K. and use of the product is the responsibility of the prescribing clinician. AIGIV may only be requested by consultant-level clinicians.

The case may be discussed with the on-call Microbiologist Consultant covering the hospital. The local ID Consultant may also be contacted.

Further advice can be obtained from the on-call Consultant:

- **Infectious Diseases Consultant**, at the **Brownlee Centre**, Gartnavel Hospital, 1053 Great Western Road, Glasgow G12 0YN  
Phone: 0141 211 1089
  - **Consultant Microbiologist**, at the **Glasgow Royal Infirmary**  
84 Castle Street, Glasgow G4 0SF, United Kingdom  
Phone: 0141 211 4000
- or
- The **Special Pathogens Reference Laboratory**,  
HPA, Porton Down, Salisbury, Wiltshire SP4 0JG  
Phone via switchboard: 01980 612100  
Email: [special.pathogens@hpa.org.uk](mailto:special.pathogens@hpa.org.uk)
- **ITU Consultant**, at the **Glasgow Royal Infirmary**  
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Following discussions, if it is agreed that the clinical criteria (appendix 1, section II.(1)) have been met, the *HPS Protocol for the Release of AIGIV in Scotland* should be followed (Appendix 2). NB. In the rest of the UK, please consult your local Health Protection Services.

### 3) 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 severe 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 from 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  $10^9$ /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.

### **III. Use of Anthrax Immune Globulin Intravenous (Human)**

#### **1) Anthrax Immune Globulin**

Anthrax Immune Globulin Intravenous (Human) (AIGIV) is intended to neutralise the circulating toxin of *Bacillus anthracis* which is a key element in the pathogenesis of anthrax infection, and if given early in the development of systemic anthrax could mitigate the effects of the disease. The following summarises the theory of the use of AIGIV, the available data from animal experiments, and the clinical usage of the drug as recommended by the US Centres for Disease Control and Prevention (CDC) and how it might be used in the UK.

#### **2) Use of AIGIV**

**AIGIV is a supplemental treatment only and MUST NOT be used to replace antibiotic therapy or debridement which remain the first line of treatment.**

Full informed consent must be obtained from the patient (or relatives, if the patient's condition precludes giving consent) and documented in the clinical notes before AIGIV is administered.

AIGIV should be given according to the schedule recommended in the CDC E-IND protocol.

*It is a condition of the use of AIGIV that objective measures and data are collected including a full assessment of the patient's clinical condition before, during and after the infusion. AIGIV cannot be issued unless the clinician is able to ensure that the conditions described in the CDC E-IND can be met.*

#### **3) Antibody Therapy for Anthrax**

Early animal experiments identified the key role of Protective Antigen (PA) in pathogenesis and suggested that antibodies to PA might be protective. As PA is the carrier molecule for the effector parts of the toxin, its removal will prevent the toxin from working as it cannot enter the target cells. Animals passively immunised with anti-PA immunoglobulin are protected if the treatment is given before or shortly after exposure; the protective value diminishes the later the therapy is given in the development of the disease.

This is to be expected: the toxin is internalised inside the target cells and is inaccessible to the antibodies, so they cannot reverse the damage to cells already affected. The loss of macrophages will also delay the immune response, as these are key cells in coordinating the body's defences. In later disease, the cycle of inflammatory damage, coagulation, vascular leakage and local hypoxia is self-perpetuating, and removal of the toxin will not reverse this process. Anthrax Immune Globulin Intravenous (Human) (AIGIV) has been demonstrated in animals and in the US case in which it was given to remove circulating toxin, and so would be expected to prevent further damage by the toxin itself.

#### **4) Anthrax Immune Globulin: Study Data**

The US CDC has produced a detailed summary of the data on AIGIV. Extracts from this document are quoted in this document with permission.

##### ***Preclinical efficacy data***

The efficacy of AIGIV has been tested in rabbits and in macaques. In the rabbit study, rabbits were exposed to anthrax by aerosol and given either no treatment, normal human immune globulin (NHIG) or AIGIV at 20 or 30 hours post infection at 15, 20 or 30 units/kg. The survival and the mean time to death were improved in a dose-dependent manner, and early treatment was significantly better than the later course. No benefit was seen with NHIG. In cynomolgus macaques, AIGIV was given at doses of 7.5, 15 or 30 units/kg to different groups of monkeys, using the appearance of detectable level of toxin with a PA assay as the indication for treatment. Again, a dose dependent response was seen, with the highest protection rate reducing mortality from 15/16 monkeys in the control group to 4/14 in the group given 30 U/kg.

##### ***Data in humans***

A clinical trial in 65 volunteers was used to determine the pharmacokinetics of the drug based on toxin neutralising activity, and also the safety profile, reported as less similar than 5% of drug-related adverse effects. The safety profile of this product is likely to be analogous to any other human immune globulin.

##### ***Presentation and dose***

AIGIV is supplied as a 50 ml glass vial, and 5-7 vials are required to give a dose of 420 Units, depending on the potency of the lot employed.

##### ***Use of Anthrax Immune Globulin Intravenous (Human) (AIGIV)***

In a clinical application therefore, the maximum benefit would be seen if Anthrax Immune Globulin Intravenous (Human) (AIGIV) were given at the earliest possible opportunity and in established sepsis there would probably be minimal benefit. AIGIV does not replace debridement and antibiotic therapy. Experience from botulinum toxin in drug users suggests that without debridement the injection site represents an ongoing source of toxin, and AIGIV does not therefore either control this or prevent relapse when the levels fall. Debridement is therefore considered an essential precursor to consideration of suitability for use of AIG treatment.

There is relatively little data on clinical efficacy of the AIGIV, and it should therefore only be used in a controlled situation where it can be monitored adequately to gauge its efficacy.

##### ***Conclusions and recommendations***

1. AIGIV may be of benefit if given early in the onset of systemic disease caused by *B. anthracis*.
2. AIGIV is unlikely to have any significant effect in well established sepsis, and cannot reverse pre-existing damage.

## **IV. Q&A Anthrax Immune Globulin Intravenous (Human) (AIGIV)**

This may be helpful when giving information to patients prior to obtaining informed consent, or discussing with relatives or partners.

### **1) What is anthrax?**

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax most commonly occurs in wild and domestic mammalian species (cattle, sheep, goats, camels, antelopes, and other herbivores), but it can also occur in humans when they are exposed to infected animals, or to tissue from infected animals, or when anthrax spores are used as a bioterrorist weapon.

### **2) What is systemic anthrax?**

Systemic anthrax is defined as a laboratory-confirmed and clinically compatible case of cutaneous, inhalation, or gastrointestinal anthrax with signs such as fever, shock, or end organ dysfunction.

For more information on the types of anthrax, please see “Q&A about Anthrax” located at: <http://www.bt.cdc.gov/agent/anthrax/faq/>

### **3) What is AIGIV?**

AIGIV stands for Anthrax Immune Globulin Intravenous (Human). It is an investigational medicine that can be used along with appropriate antibiotic therapy and debridement where applicable to treat patients with systemic anthrax. The medicine is derived from plasma obtained from donors immunized with the anthrax vaccine. AIGIV contains antibodies that help remove part of a toxin from *Bacillus anthracis*, the bacteria that causes anthrax. While antibiotic therapy, such as ciprofloxacin or doxycycline, kills *B. anthracis* bacteria, AIGIV targets the toxins made by this bacteria.

### **4) Who is eligible to receive AIGIV?**

People with systemic anthrax may be eligible. The AIGIV recipient must also be receiving appropriate antibiotic therapy and should continue to receive antibiotics before, during, and after AIGIV administration. AIGIV is given only as an additional therapy and is not a substitute for treatment with the recommended antibiotic therapy.

### **5) Who should NOT receive AIGIV?**

People who have systemic anthrax who should NOT receive AIGIV are those with immune globulin A (IgA) deficiency or a history of a severe allergic reaction to a hyper-immunoglobulin product. Intravenous immune globulin (human) products have been reported to produce renal dysfunction (kidney problems) in patients that are predisposed to acute renal failure. It is recommended that renal function be assessed prior to administration of AIGIV and at appropriate intervals following administration, especially for patients at risk of developing acute renal failure.

### **6) What are the benefits of AIGIV?**

AIGIV may help save the patient's life from the anthrax disease. However, **we do not know** for certain that it will help.

### **7) Is AIGIV licensed by the US Food and Drug Administration (FDA)?**

No, AIGIV is not licensed by the FDA; it is experimental and must be administered under an Emergency use Investigational New Drug protocol (E-IND). It is not specifically licensed for use in the UK. Therefore, the AIGIV recipient or a family member, as appropriate, must provide informed consent for the drug to be used.

For more information on E-IND, see question below *What is an Emergency Use Investigational New Drug protocol* and/or visit [www.fda.gov](http://www.fda.gov).

### **8) What is an Emergency use Investigational New Drug (E-IND) protocol?**

The legal use of AIGIV strictly follows a regulated E-IND protocol. An Investigational New Drug (IND) application is needed to distribute and administer an FDA unapproved medical product. The IND application is completed and submitted to the FDA. An E-IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

Only AIGIV produced under conditions acceptable to the FDA will be offered and released for emergency use under an FDA-authorized Emergency Investigational Drug Application (E-IND) for emergency administration to persons with systemic anthrax as an adjunct therapy.

### **9) What are the possible risks of AIGIV administration?**

- The injection site may experience some discomfort, bleeding, or bruising. Rarely, fainting or local infection may happen. The risk of infection is very small but if it happens, medication will be given to help fight the infection.
- Since AIGIV is made from human blood, it may carry other organisms such as a virus. The people who gave blood for AIGIV were carefully tested. They tested negative for many of the organisms that are known to be passed to people through blood, such as the AIDS virus, hepatitis, and syphilis. The process used to make the AIGIV kills viruses that are known to cause disease in people. It is not known if there are other viruses that are not killed by this process that could lead to sickness.
- Some people may have an allergic reaction to AIGIV. Signs of an allergic reaction are: trouble breathing, closing of the throat, swelling of the tongue, hands, or feet, urticaria ("skin rash"), and feeling like the patient will pass out.
- Fevers, muscle pains, lower back pain, nausea, or vomiting may occur after getting AIGIV. If this happens, the doctor can slow down the speed that AIGIV is given, or the doctor can give drugs to help stop these problems. People with certain conditions such as "IgA Deficiency" can have more severe problems. Patients with "IgA Deficiency" should NOT receive AIGIV.
- A few people who have been given antibodies for other diseases have had kidney problems and kidney failure. While this is unlikely to happen, if kidney problems have occurred in the past or during infection with anthrax, there is a chance that AIGIV treatment could make those problems worse.
- A few people who have been given antibodies for other diseases have had swelling of the fluid and tissues around the brain and the spinal cord. People who get this side effect

from getting antibodies usually have a bad headache and a stiff neck. Their symptoms usually go away completely after the antibody treatment is stopped.

- A few people who have been given antibodies for other diseases have had problems with blood clots.
- A few people who have been given antibodies for other diseases have had strokes or heart attacks. This happens mostly in older people, and in persons with heart, blood and blood pressure problems. The chance of having these problems from antibody treatment can be reduced by giving the treatment very slowly.
- There may be other mild or even serious problems from AIGIV that we do not yet know about.

## V. References

Anthrax Immune Globulin Intravenous (Human) Investigational New Drug Protocol (Version 1.0). BB-IND 13026. January 7, 2010.

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## Appendix 2

# Protocol for the Use and Release of Anthrax Immune Globulin Intravenous (Human) (AIGIV) in Scotland

This Protocol is available in the restricted part of the HPS Anthrax website - <http://www.hps.scot.nhs.uk/anthrax/resources.aspx>. Please [login](#) to view. Anyone involved in case management of these patients who requires access to the restricted part of this website should contact their board public health team for [login](#) details.