REVIEW ARTICLES

Injectional anthrax among people who inject drugs and implications for research in Vietnam: a literature review

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Abstract

Anthrax is a serious zoonotic disease caused by Bacillus anthracis, which primarily affects herbivorous wildlife and domestic livestock, and occurs nearly worldwide. Anthrax was classified into inhalational anthrax, gastrointestinal anthrax and cutaneous anthrax. More recently, injectional anthrax has been added as the forth type of anthrax infection. This paper aims at 1) summarizing the characteristics of injectional anthrax; 2) exploring the possibility of acquiring anthrax among people who inject drugs (PWID) in Vietnam; 3) discussing the implications for anthrax surveillance in the PWID community and future research in Vietnam. Literature review method is employed using publications and gray literatures available per literature search. The results show demographic, clinical and sub-clinicalcharacteristics of injectional anthrax among PWID in the world. Possibility of the disease occurrence among Vietnamese PWID was not conclusive due to limited publications in the world and no publication on injectional anthrax in Vietnam, however, further research and surveillance requiring sufficient awareness of clinicians and enhancement of laboratory capacity should be implemented to provide more evidence.

Keywords: *Injectional anthrax, anthrax, injecting drug users (IDUs), people who inject drugs (PWID), Vietnam*

1. Introduction

Anthrax is a serious zoonotic disease caused by *Bacillus anthracis* (*B. anthracis*), a gram-positive, spore-forming bacterium. The disease primarily affects herbivorouswildlife and domestic livestock, and occurs nearly worldwide; highest rates occur in countries where anthrax vaccine is not available for widespread livestock vaccination [1]. Human anthrax is less common and often happens when people come contact infected wild herbivores or domestic livestocks, or their product such as skin, meat, hides, bones etc. Therefore, farmers, veterinarians, people who handle animal products, laboratory professionals are at higher risk of the disease [2]. Since 2001, *B. anthracis* has been considered as a leading potential agent for biowarfare and bioterrorism that mail handlers, soldiers, field epidemiologists and similar-work personnel may be exposed to anthrax spores during a bioattack [3].

Classically, anthrax was classified into three types based on the route of infection including inhalational anthrax (inhaling spores of bacterium), gastrointestinal anthrax (consuming in-

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Received 05 April 2019; In revised form 25 June 2019; Accepted 29 July 2019

fected meat, contaminated water) and cutaneous anthrax (via skin lesion) [1]. More recently, injectional anthrax was defined as the forth type of anthrax exposure. An initial case occurred in Norway in 2000 in a PWID who admitted to hospital with some symptoms of soft tissue infection, complications of septic shock, meningitis and death [4]. Injectional anthrax was distinguished from cutaneous anthrax due to the alternative symptoms (site infection vs systemic infection) and severity of injectional anthrax. The injectional infection can cause case-fatality rates of 34%-47% among its infected patients despite antibiotic treatment while the rate wasless than 1% among cutaneous anthrax patients with proper antibiotic treatment [5–8].

Surveillance across seven European countries between 2000-2010 showed that *B. anthracis* accounted for 4.1% of spore-forming bacterial infections [9]. There were two outbreaks of injectional anthrax among PWID in 2009 in the United Kingdom (mostly in Scotland) and Germany in 2012 [5, 7]. There were two hypotheses posited for how heroin was contaminated with *B. anthracis* spores. First, drug was contaminated during transportation from the source country to destination countries. Second, contamination occurred during the drug mixing process by drug users, but this remained unproven. It was evident that the pathogens came from the same batch of heroin imported from Afghanistan, where more than 70% of the global opium products in 2012 were produced and distributed via many different routes [10]. In addition, a study employing strain-specific single-nucleotide polymorphism (SNP) assays, which was developed based on whole genome of a representative *B. anthracis* strains from a heroin user (Ba4599), showed that all the strains from *B. anthracis*-polymerase chain reaction (PCR) positive patients shared the Ba4599 SNP genotype [11]. Phylogeographic analysis also indicated the close relation between Ba4599 strains and strains from Turkey that was not related to strains isolated in Scotland or Afghanistan [11]. Therefore, it suggested contamination of heroin in Turkey, on the way from Afghanistan to destination countries in Europe, because the drug was wrapped/hidden in animal hides and bones, which might be already contaminated with the spores [11–14]. As of 2014, no case of injectional anthrax have been reported in China [15].

In Vietnam, clinical cases of anthrax are mostly reported in the northern mountainous regions where livestock grazing and trading at the border with China and Laos are common. The number of clinical cases ranged between 12 and 201 cases per year in the period of 2000-2014, and most of those were cutaneous anthrax [16]. To date, injectional anthrax among PWID has not been reported in Vietnam. As of 2012, size estimation based on numbers of PWID mentioned in reports of Ministry of Labour-Invalids and Social Affairs shows that the population of PWID ranged between 111,233 and 273,579 people [17]. Thus, assuming the more conservative estimate, there may be more than 100,000 people at risk of injectional anthrax in Vietnam. The PWID are highly concentrated in some hotspots and those are located in large cities throughout the country [17–19]. Needle sharing behaviour is still common among the PWID in Vietnam, which may increase the risk of injectional anthrax if contaminated drugs enter the country [20].

This paper summarizes the characteristics of injectional anthrax. Additionally, we explore the possibility of acquiring anthrax among PWID in Vietnam. We also discuss the implications for anthrax surveillance in the PWID community and future research in Vietnam.

2. Methods

A literature review was employed to synthesize available peer reviewed and gray literature based on the following criteria:

Search strategy: peer reviewed publications and gray literature were searched in the databases including MEDLINE/PubMed, Google Scholar (English), websites of Ministry of Health *(https://www.moh.gov.vn/)*, General Department of Preventive Medicine *(http://vncdc.gov.vn/)*, Google (Vietnamese) etc with the following key words:"anthrax","Bacillus anthracis", "B.anthracis", "injectional anthrax", "injecting drug users", "IDUs", "people who inject drugs", "PWID", "bệnh than", "nghiện chích ma tuý". Boolean operators including AND, OR and NOT were used to make combination of the key words. Medical Subject Headings (MeSH) of National Library of Med-

icine, National Institute of Health (NIH, US) was also used during literature search.

Pre-defined exclusion criteria for literature search were applied: anthrax in animal, in vitro study, studies on vaccine, and laboratory techniques were excluded.

All articles (peer reviewed and gray) were checked for duplication, full-text availability, and summarized for further analysis.

3. Content

Literature search results

In total, 732 documents were found on MEDLINE/PubMed and Google Scholar, there was no gray literature related to topic of study found on the websites. After title screening, 317 documents were excluded due to duplication (1) and irrelevance of study topic (316), leaving 415 documents for further abstract screening. In the step of abstract screening, 390 documents were not included due to pre-defined exclusion criteria, 1 paper without laboratory confirmation of anthrax, thus 24 documents were used for further analysis. Among the 24 documents, there were 4 papers that reported two events of injectional anthrax in Scotland and Germany, however, the papers were not totally duplicated so that they were used separately as independent papers. Eight papers with case report or case series study design and 16 papers with other study designs (case-control, cross-sectional, literature review). All of studies included in this review were conducted from 2000 up to the present and in European countries. None of the papers were from Vietnam or other Southeast Asian countries. Figure 1 shows the results of literature search.

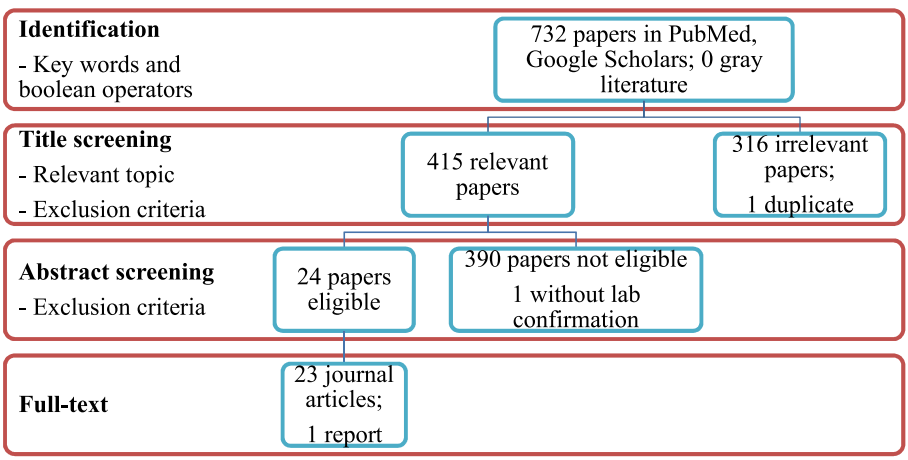

Fig.1. *Flowchart of literature search*

Demographic characteristics of injectional anthrax patients

After the first case of injectional anthrax reported in Norway in 2000 [21], there were two additional reported outbreaks in the United Kingdom and Denmark in 2009-2010 [22–25] and in Germany in 2012 [5, 26, 27].

Age and gender information were not available for all patients in case report or case series studies, but for those available, the age of patients ranged between 28 and 55 years old; and there were more males than females. Only one case in Norway and one case in Germany were reported with drug administration by skin-popping (drug is injected under skin) that is different from others with intravenous drug use (drug is injected directly to their vein) (see annex 1). The studies in Scotland also supports that the cases aged from 18 to 55 years, with median of 34-35 years, slightly older than median age of PWID in general, and 68-70% of the patients were males [6, 14, 28–30]. The age and gender attribution of cases with injectional anthrax among PWID were similar to cases with other skin infections in this population [31].

The predominance of males among anthrax patients is reasonable when 70% of PWID in Europe were males [32, 33]. A systematic review also indicates that 58.2% and 70.2% of PWID in Eastern Europe and Western Europe were 25 years or older, respectively [33]. Though it was not statistically significant, the patients survived the course of disease in Scotland seemed younger than those who did not survive (31.9 + 1.9 years and 38.2 + 2.8 years, respectively) [28].

The longer a drug user injected, the more likely he/she got infected with injectional anthrax. A case-control study in Scotland in 2009 showed that PWID with 10 years or more experience of injecting drug use were 2.43 times more likely to be infected (95%CI: 1.31 – 4.52) than those with shorter history of injecting drug use [30].The likelihood of injectional anthrax infection was greater among PWID with opioid substitution therapy (OST) than the others (adjusted OR = 2.74; 95%CI, 1.40–5.37). PWID who reported smoking-only behaviour had less likelihood of acquiring injectional anthrax (adjusted OR = 0.42, 95%CI: 0.20 – 0.86). Alcohol misuse was not associated with the status of being patients of injectional anthrax [14, 30].

Clinical and sub-clinical characteristics of injectional anthrax patients

The progression of injectional anthrax was rapid, most of the patients in case reports admitted to hospital within 2-5 days after injecting contaminated drugs, no matter where the injection site was. Furthermore, in cases of misdiagnosis and improper treatment, patients experienced more severe disease with compartment syndrome, septicaemia, necrosis, and multi-organ failure and then died within 1-3 days of hospital admission (*see annex 2*). The symptom onset occurred within 1-2 days after drug injection. A case-control study in Scotland supports a finding that 40% of laboratory confirmed/probable injectional anthrax cases got the symptoms in one day or less after injection [14]. Another study of 31 patients, also in Scotland, in 2009 showed the evidence that injectional anthrax pathology occurred in two phases [34]. The first phase was from hospital admission until completion of debridement surgery that the patient would be seen to recover well, but quickly, he/she came to the second phase after 24-72 hours later with septic shock, multi-organ failure [34]. It requires intensive care with thorough monitoring and readiness of supportive equipment.

Although the signs and symptoms of injectional anthrax were not consistent for all the patients, increasing and extending swelling, reddening and pain of drug injection site were the most common symptoms among the patients. They were also the reasons for seeking medical care *(see annex 2)*. The case-control study in Scotland also gave the same results that 86% of 119 anthrax cases in drug users had localised swelling, followed by pain in 84% of the cases. In addition, this study indicated other common signs and symptoms like malaise (74%), fever (65%), anorexia (52%), nausea (52%) and leaking infection site (52%) among laboratory confirmed anthrax cases [14]. However, those symptoms are not specific for injectional anthrax but also common for many other bacterial infections [35, 36], so the suspicion of the disease should also base on other clinical manifestations, sub-clinical results and history of injecting drug uses with injection sites closed to the sites of symptoms.

In contrast to more frequently occurred signs and symptoms mentioned above, oedema occurred less commonly but in very severe cases. Eschar formation (specific sign for cutaneous anthrax) was not mentioned in any case report and also supported by studies in European countries [37, 38]. Other symptoms reported with lower frequency include deep vein thrombosis, erythema, blistering formation, and abnormal blood pressure (*see annex 2*).

An analysis comparing the signs and symptoms between survivors and non-survivors of injectional anthrax in Scotland from 2009-2010 showed that pains and swellings were the most common symptoms for both groups, however, the degree of the symptoms were different between the two groups. Non-survivors were reported with more generalized symptoms while the survivors reported localized symptoms at the injection site [28].

Leukocytosis was not seen for most of the patients in the case reports. This may be because oedema toxin (one of three toxins involved in anthrax infection) inhibits the movement and kills macrophages, and then reduces

phagocytosis. The toxin also limits the expression of cytokines that would impair the innate and adaptive immune responses to anthrax infection as cited by Mogridge (2007) [39].

Other sub-clinical indicators included anaemia, thrombocytopenia, elevated procalcitonin, hypokalaemia, elevated liver enzymes, and lowered coagulation parameters, however, they were not common and usually occurred with the complication of the disease *(see annex 2)*. Another noticeable indicator was D-dimer, a protein fragment present in the blood after a blood clot is degraded by fibrinolysis [40], which was extremely high in three patients, of whom two died on the day of hospitalization [5, 27]. The increase in blood D-dimer is a good marker for identification of some serious health conditions with intravascular coagulation including deep vein thrombosis (DVT) [40, 41], which can be caused by *B. anthracis* infection [42, 43]. A study on animal proved the association between the elevation of D-dimer following lethal toxin treatment and the initiation of coagulation [44].

Across the studies, confirmatory test results were mainly based on three techniques including Gram stain, polymerase chain reaction (PCR), and bacterial culture from blood or tissue samples. PCR was used as confirmation for *B. anthracis* infection in lesion samples collected from the patients or positive bacterial cultures. Other techniques included isolation, molecular typing, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF), multilocus variable-number tandem repeat analysis (MLVA), and single nucleotide polymorphism (SNP). Further analysis with MLVA and SNP typing showed the close relationship between strains of *B. anthracis* collected from the patients in Germany, Denmark in 2012 and strains collected from previous outbreaks in the United Kingdom 2009-2010 [25, 27]. It supports the hypothesis of a single source of *B. anthracis* from the same batch of heroin.

Though the data on what drugs, other treatment methods was not available for fatal cases, the treatment could be successful when combining multiple antibiotics and supportive treatment. According to the case reports/series, the most common antibiotics used in injectional anthrax included intravenous clindamycin, metronidazole, and ciprofloxacin. Besides, penicillin/benzylpenicillin was prescribed after susceptibility testing showed that *B. anthracis* was susceptible to this group of antibiotics. Supportive treatment included using Negative Pressure Wound Therapy device for patients with compartment syndrome (*see annex 3*).

Possibility of acquiring injectional anthrax among PWID in Vietnam

Southeast Asia is a hotspot for drug trafficking and drug use with significant amount of heroin seizure and a high number of drug users [45]. Furthermore, beside mass local production in this region (mostly in Laos PDR and Myanmar according to the available data), the drug was also imported from Afghanistan via its neighbouring country (i.e Pakistan) [10, 46, 47]. In Vietnam, the government has committed resource and effort to eradicate the cultivation of opium poppy and production of opium. Between 2007 – 2015, more than 300 hectares for opium poppy cultivation in the country was eradicated [45]. Since the local production is strictly eradicated, the drug circulating in Vietnam might be trafficked from other countries in the region and from Afghanistan via countries bordering Vietnam. Either the drug was imported from local production in Southeast Asia or from other regions, it poses the risk of injectional anthrax to PWID in Vietnam which is similar to what happened in the Europe during the outbreaks in 2009-2012. Firstly, drug imported from other countries could be contaminated during transportation like it was on the way from Afghanistan to European countries [11–14]. Secondly, the circulation of anthrax in human and domestic livestock in Vietnam and its bordering countries could be another factor for the contamination of heroin with *B. anthracis* spores during transportation, distribution, and mixing/processing [41, 48].

The estimation for 2016 showed that there were 3.28 million (2.32 – 4.01 million) drug users in East and Southeast Asia regardless of the route of drug administration. The figures for PWID in the region were 2.21 million people (3.20 – 4.19 million) [45]. According to the World Drug Report in 2013, Vietnam was the third country with highest growing number of PWID with approximately 200.000 people [10].

That estimate is in line with the range reported above for Vietnam in 2012 [17]. This indicates a large population with an elevated risk of many serious infectious diseases including HIV/AIDS, viral hepatitis C and possibly injectional anthrax, particularly when the needle and syringe sharing behaviours are still common among Vietnamese PWID (6.3% in Hanoi, 18.1% in Ho Chi Minh city, and 55.7% in An Giang province as cited by Thanh *et al*. 2015) [20]. The North West region and North East regions of Vietnam consist of provinces bordering with China and Lao PDR, where most of the clinical cases of anthrax in northern mountainous region were reported [16]. The number of PWID in North West and North East regions was also estimated in low and high estimate scenarios in 2012. For low estimate scenario, the number of PWID was 27,496 and 4,927 people for North West region and North East region, respectively. In high estimate scenario, it was 58,267 and 20,945 PWID lived in North West region and North East region, respectively [17].

The studies in Europe indicated that the injectional anthrax patients admitted to hospitals with the symptoms of soft tissue infections, which could be similar to other skin infections among PWID [30, 37]. The data on injectional anthrax and skin infections or soft tissue infections among PWID in Vietnam are not available for analysis. However, the high percentage of death with unknown cause in the PWID may be suggestive further investigation including testing for *B. anthracis* and other spore-forming bacterial infections. A study in Thai Nguyen province revealed that 18% of death among male PWID remained unknown of the cause [49].

With limited available literature globally and no literature published in Vietnam on injectional anthrax, it is difficult to conclude whether it has occurred or not in Vietnam. Nevertheless, it may be underreported due to many factors such as misdiagnosis/misclassification in clinical cases with other similar skin/soft tissue infections and insufficient laboratory capacity for identification of anthrax, particularly in northern mountainous region of Vietnam. Thus, raising doctors' awareness of injectional anthrax among PWID and improvements of capacity for identification of the pathogen will be essential for further research to provide more evidence on this topic in Vietnam.

4. Conclusion

The demographic characteristics of injectional anthrax patients were fairly similar to common PWID community. However, male and older PWID with longer experience of injecting drug use were at higher risk of the infection. The clinical and sub-clinical characteristics showed the similarity with other skin/soft tissue infections that could lead to misdiagnosis at admission of the cases. It also suggested the diagnosis to be based on clinical manifestations, sub-clinical results and history of injecting drug use. Although it is not conclusive about the possibility of contracting injectional anthrax in Vietnamese PWID, it implies further surveillance and research among this large population who are exposing to similar risk of infection to those in European countries.

Acknowledgment: Jason K. Blackburnwas supported by the US Defense Threat Reduction Agency's Biological Threat Reduction Program.

Conflict of interest: none.

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Annex 1. *Demographic characteristics of injectional anthrax patients from case report/case series*

Study	Time	Country	Age	Sex	Other characteristics
Soft tissue infections caused by spore-forming bacteria in injecting drug users in the United Kingdom [21]	2000	Norway	49	Male	Skin-popper
A case of septicaemic anthrax in an intravenous drug user [22]	2009	The UK	32	Male	Intravenous drug user
Injection anthrax causing compartment syndrome and necrotising fasciitis [23]	2010	The UK	28	Female	Intravenous drug user
Subcutaneous anthrax in three intravenous drug users [24]	2010	The UK	44	Male	Intravenous drug user
			36	Male	Intravenous drug user
			32	Female	Intravenous drug user
Two anthrax cases with soft tissue infection, severe oedema and sepsis in Danish heroin users [25]	2010	Denmark	55	Male	Methadone maintenance therapy
	2010	Denmark	39	Male	Intravenous drug user
Anthrax cases among injecting drug users Germany [26]	2012	Germany	N/A	Male	Intravenous and intramuscular injections
	2012	Germany	N/A	N/A	
Fatal anthrax infection in a heroin user from southern Germany, June 2012 [27]	2012	Germany	~50	N/A	
	2012	Germany	N/A	N/A	
	2012	Germany	N/A	N/A	
Injection Anthrax—a New Outbreak in Heroin Users [5]	2012	Germany	N/A	N/A	
	2012	Germany	N/A	N/A	Multiple drug dependency

Annex 2. *Clinial and sub-clinical characteristics of injectional anthrax in case reports/case series*

Study	Duration before admission	Clinical symptoms				Sub-clinical symptoms	
		Swelling	Oedema	Pain	Others	WBCC	Others
Soft tissue infections caused by spore-forming bacteria in injecting drug users in the UK [21]	4 days	N/A	Muscles and subcutaneous tissues in buttock, thigh and lower abdominal wall	N/A	Meningitis on lumbar puncture Gluteal region, thigh, and lower abdominal wall were erythematous No eschar formation No pus or necrosis	5 x 10^9/L in CSF 25.6 x 10^9/L in serum	
Injection anthrax causing compartment syndrome and necrotising fasciitis [23]	5 days	Extending from fingers to right shoulder	N/A	Increasing	Tachycardic	N/A	
Subcutaneous anthrax in three intravenous drug users [24]	10 days	Yes	Yes	Increasing	Compartment syndrome Erythema distal to the injection site Copious serous fluid was present throughout the wound	N/A	
	3 days	Considerable	N/A	Finger movements were painful and restricted	Markedly hypoalbuminaemic	≤9.1 × 10^9/L	CRP ≤ 9 mg/L Sodium and albumin levels remained normal
	3 weeks	Yes	Spreading	N/A	Suspected abscesses in both lower limbs Necrosis and fibrosis with free fluid There was asymmetry between the hands	≤7.4 × 10^9/L	CRP ≤ 6 mg/L Sodium levels remained normal

A case of septicaemic anthrax in an intravenous drug user [22]	12 hours	Increasing in left leg	N/A	N/A	Erythematous sinuses in both groins Purulent discharge from a chronic sinus in his left groin Left sinus was discharging foul smelling pus Tachycardia Blood pressure 136/86	15.9 × 10^9/L	CRP of 2.1 mg/L CT scan of abdomen, pelvis and thighs showed loculated fluid and inflammatory
Anthrax cases among injecting drug users Germany [26]	N/A	N/A	N/A	N/A	Infected injection site Anthrax septicaemia	N/A	
	3 days	At injection site	N/A	N/A		N/A	
Fatal anthrax infection in a heroin user from southern Germany, June 2012 [27]	2 days	Swelling Reddening at injection site	N/A	N/A	Nausea and dyspnoea Respiratory failure	15.9 x 10^9/L	Anaemia Thrombocytopenia Elevated procalcitonin Hypokalaemia Elevated liver enzymes Lowered coagulation parameters Exhigh levels of D-dimers
	N/A	N/A	N/A	N/A	The patient is stable under antibiotic therapy after surgical debridement	N/A	
Injection Anthrax—a New Outbreak in Heroin Users [5]	2 days	Swelling, Reddening at injection site	N/A	N/A	Nausea Shortness of breath Increasing respiratory insufficiency	Leukocytosis	Anemia Thrombocytopenia Increased procalcitonin Hypokalemia Extremely high D-dimer

	N/A	Swelling Reddening	N/A	N/A	Cutaneous necrosis Blistering formation on the lower limbs Headaches Dry cough Pneumonia with uneven presentation, pleural effusion	N/A	Radiological examination showed significant increased streaking in the lungs with no circumscribed infiltrate
	4-5 days	Progressive swelling Reddening	N/A	Whole right arm	Blistering, primarily in the cubital region Suspected deep vein thrombosis following IV injection	N/A	Markedly high D-dimer Thrombosis was ruled out using a chest CT
Two anthrax cases with soft tissue infection, severe oedema and sepsis in Danish heroin users [25]	N/A	Swelling of the right thigh	Severe oedema of the lungs on chest x-ray	Abdominal pain	Abdominal compartment syndrome Sweating Tachycardia Vomiting Septic shock with multi-organ failure	N/A	CRP levels in serum were low CT scan showed mucous masses Severe metabolic acidosis, pH 6.99
	N/A	Swelling of right arm	Substantial	N/A	Skin was tense and discoloured, involve most of the body Blood pressure was fluctuating	N/A	Ultrasonographic examination showed diffuse soft tissue swelling

N/A: not available; WBC: White blood cell count

Annex 3. *Treatment and outcome of injectional anthrax in case reports/case series*

Study	Drugs	Outcome
Soft tissue infections caused by spore-forming bacteria in injecting drug users in the United Kingdom [21]	Dicloxacillin High-dose penicillin, chloramphenicol and dexamethasone	Dead
Injection anthrax causing compartment syndrome and necrotising fasciitis [23]	Intravenous benzylpenicillin, clindamycin, ciprofloxacin, and metronidazole for 4 weeks Oral ciprofloxacin in order to complete a 60-day course	Survived with multi-compartment fasciotomy
Subcutaneous anthrax in three intravenous drug users [24]	Intravenous benzylpenicillin and flucloxacillin Intravenous ciprofloxacin, benzylpenicillin and clindamicin	Discharged after 60 days of in-patient care
	Intravenous ciprofloxacin, clindamicin, benzylpenicillin and metroniadazole	Survived
	Oral flucloxacillin but not responded	N/A
A case of septicaemic anthrax in an intravenous drug user [22]	Vancomycin, Clindamycin, Ciprofloxacin, Gentamicin and Metronidazole Vancomycin, Ciprofloxacin and Clindamycin continued for 14 days 4 week course of oral Ciprofloxacin	Survived
Anthrax cases among injecting drug users Germany [26]	N/A	Dead
	N/A	N/A
Fatal anthrax infection in a heroin user from southern Germany, June 2012 [27]	N/A	Dead
	N/A	Dead
Injection Anthrax—a New Outbreak in Heroin Users [5]	N/A	Dead
	Intravenous clindamycin, metronidazole, cefazolin Penicillin G4 plus clindamycin and ciprofloxacin IV Carbapenem	Three weeks of inpatient care. Continue to receive outpatient care
	Tavanic Clindamycin Doxycycline after a rash appeared Ciprofloxacin monotherapy due to severe recurrent nausea	N/A
Two anthrax cases with soft tissue infection, severe oedema and sepsis in Danish heroin users [25]	Intravenous cefuroxime and metronidazole Changed to meropenem, ciprofloxacin and metronidazole Meropenem and ciprofloxacin dose was increased, and clindamycin was added	Dead

	Cefuroxime Dalterapin Intravenous meropenem, metronidazole and moxifloxacine Moxifloxacine Hydroxychloroquine was used to inhibit the effect of the *B. anthracis* toxins Clindamycin and ciprofloxacin Benzyl penicillin and ciprofloxacin Oral amoxicillin-clavulanate	The patient continued to improve and discharged on day 29

N/A: not available