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CASE REPORT

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Iatrogenic *Staphylococcus aureus* septicaemia following intravenous and intramuscular injections: clinical course and pathomorphological findings

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Abstract The clinical course, autopsy and histological findings are presented from three (one 33-year-old female and two males aged 26 and 56) fatalities resulting from injection therapy which has produced *Staphylococcus aureus* septicaemia. The autopsies were performed within 2–4 days postmortem. No primary focus other than the insertion site of the peripheral venous catheters or the intramuscular injections, representing the initial entry site of *Staphylococcus aureus*, could be identified. Death was attributed directly to the staphylococcal infection as a result of iatrogenic injection therapy for the treatment of a non-severe underlying illness (premature labour pains, acute loss of hearing, lumbago). The forensic diagnosis of *Staphylococcus aureus* septicaemia following iatrogenic injections has to be critically evaluated and can be established routinely in cases with delayed autopsy only when no other cause of death is revealed by autopsy, no apparent source of infection other than the insertion site can be detected and careful attention is paid to histological and bacteriological findings. All doubtful cases of nosocomial bloodstream infections with fatal outcome should undergo an immediate autopsy. In cases of very early forensic involvement microbiological investigations, including phagotyping, molecular biological characterization and identification of bacterial toxins from micro-organisms out of appropriate specimens obtained postmortem, could be efforts of potential evidential value regarding the aetiological proof. To optimize aetiopathogenetic conclusions concerning a causal relationship between iatrogenic injections and septic complications, the medicolegal investigation should also include an interdisciplinary co-operation with consultants from other relevant fields (e.g. microbiology and hygienics).

Key words *Staphylococcus aureus* · Iatrogenic injection therapy · Septicaemia · Peripheral venous catheter · Intravenous injection · Intramuscular injection

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Introduction

Septicaemia can be the most severe and life-threatening complication of iatrogenic injection techniques in use for therapeutic or diagnostic purposes [9, 13]. The presumptive clinical diagnosis of iatrogenic injection-induced infections can be difficult in the absence of signs of inflammation around the insertion site of an intravenous catheter or the puncture site of an intramuscular injection [2, 7, 16, 27, 35]. Such a diagnosis is even more difficult to establish when information about the preceding iatrogenic injection therapy is lacking [32].

Among a broad spectrum of micro-organisms causing nosocomial bloodstream infections, including Gram-positive bacteria, Gram-negative bacilli and fungi, *Staphylococcus aureus* is the most frequent micro-organism isolated in iatrogenic injection therapy-related septicaemia [2, 14, 27, 30] and staphylococcal septicaemia more frequently has a fatal outcome than septicaemia caused by other bacteria [1, 10]. Such fatalities due to *Staphylococcus aureus* septicaemia have only been reported sporadically in the forensic medical literature [16, 32].

The aim of the current study was to correlate autopsy findings in three cases of fatal iatrogenic injection therapy-related *Staphylococcus aureus* septicaemia with the preceding clinical course and to demonstrate histological findings which assist in proving a direct causation. The objective of the present study was not to discuss aspects of clinical misdiagnosis, therapeutic delay or medical malpractice. For detailed information on the well-known factors influencing the prevalence, morbidity and mortality of nosocomially acquired septicaemia (e.g. type and duration of catheterization, the widespread use of antibiotics resulting in multiple antibiotic resistance, procedures of skin preparation before insertion of intravascular devices or regimens for catheter site care), we refer to the comprehensive clinical literature on these topics [7, 10, 14, 15, 17, 21, 22, 27, 30, 31].

Case reports

Case 1

Clinical course

A 33-year-old woman was admitted to the department of obstetrics with premature labour pains in the 27th week of pregnancy. On arrival, suppression of premature labour (fenoterol) was started via a peripheral venous catheter sited in the right basilar vein and 10 days after admission the patient developed mild fever with a temperature of up to 37.8 °C. Her right arm was swollen and because of the clinical diagnosis of peripheral phlebitis, the intravenous catheter was removed. The insertion site of the catheter showed mild erythema but no suppuration. The arm was cooled with ice packs and another peripheral intravenous device was placed on the other arm. Within 2 days, the fever and signs of inflammation disappeared. The patient's condition and the course of pregnancy were uneventful for the following 25 days. On the 37th day in hospital the patient showed a recrudescence of fever with the body temperature rising to 38.5 °C and leucocytosis. Signs of phlebitis were now present on the left arm, where the intravenous catheter was now placed. The catheter was removed, the affected arm was cooled with ice and antibiotic therapy with amoxycillin was started empirically. Duplex sonography failed to confirm the clinically suspected thrombophlebitis. Subsequent blood cultures were positive for *Staphylococcus aureus* and the antibiotic regimen was changed. A diagnosis of an intrauterine infection with placentitis was made and the patient was submitted for an emergency Caesarean section. On day 39 the patient gave birth to a healthy female infant of normal size and weight. Postoperatively, the fever disappeared but the following day the patient complained of nausea and chest pain; the nausea was attributed to the general anaesthesia and the chest pain was explained by the beginning of lactation. When the chest pain intensified, the patient was transferred to the Intensive Care Unit suffering from rapid progressive tachycardia and dyspnoea. The electrocardiogram and laboratory analysis revealed an acute myocardial infarction. Despite appropriate intensive care the patient died on hospital day 41.

Autopsy findings

Autopsy revealed an acute suppurative endocarditis with vegetations on the aortic valve. A coronary embolism of the anterior descending branch of the left coronary artery with an acute myocardial infarction of the anterior wall of the left ventricle and the anterior interventricular septum was found. Multiple microabscesses in both kidneys and an acute splenitis were observed. No inflammatory changes of the basilar veins were found. Postmortem blood cultures and specimens taken for culture from the aortic valve grew *Escherichia coli* and *Enterobacter cloacae* which were attributed to postmortem contamination.

Histological examination

The aortic valve showed fibrinous vegetations with Gram-positive cocci (Gram stain) but no signs of underlying rheumatic heart disease (Fig. 1). Histologically the anterior descending branch of the left coronary artery showed an occlusive embolism of the lumen with polymorphonuclear infiltration of all coats of the vessel wall adjacent to the embolization (Fig. 2). In the myocardium, coagulative necrosis with loss of nuclei and interstitial infiltration of granulocytes without onset of fibroplastic response was found. The kidneys showed multiple microabscesses with neutrophilic exudate within tubules and renal parenchyma.

Cause of death

Death was attributed to acute myocardial infarction following coronary embolism due to infective endocarditis secondary to *Staphylococcus aureus* septicaemia following peripheral venous catheterization.

Case 2

Clinical course

A 26-year-old, previously healthy male was referred to the ENT ward of a major hospital with acute loss of hearing. Hemodilution infusion therapy (dextran) was started via a peripheral venous catheter, placed in the left basilar vein. On day 4, the patient complained of nausea, vomiting and dyspnoea and the body temperature was intermittent between 37.4 °C and 40 °C. The patient's left arm, where the peripheral venous device was located, was painful, swollen and erythematous. As a consequence, the intravenous catheter was removed. The arm was cooled and the patient received paracetamol. On day 5 the patient remained febrile with a body temperature of 40.4 °C and showed tachypnoea (50–60 breaths/min) and tachycardia (140 beats/min). On the presumption of a septic phlebitis, blood cultures were performed. The patient was transferred to the Intensive Care Unit immediately for hemodynamic monitoring and supportive therapy including central venous infusion therapy with hydroxyethyl starch, heparin and antibiotics (flucloxacillin and cefazolin). Chest radiography revealed multiple nodular infiltrates in both lungs. On day 5, the blood pressure decreased to 70/30 mm Hg and a tachycardia of 180 beats/min was present. Arterial blood gas measurement revealed metabolic and respiratory acidosis. Despite endotracheal intubation, mechanical ventilation and supportive therapy with dopamine hydrochloride, the patient died on day 6. Blood cultures identified *Staphyloccocus aureus* strains sensitive to the administered antibiotics but the culture results were not available until 4 h after death.

Autopsy findings

At autopsy, multiple foci of purulent pneumonia were found in both lungs with fibrinous and suppurative pleurisy. Additionally, an acute splenitis was found. A mild oedema surrounding the vascular wall of the left basilar vein where the intravascular device had been placed was noted, but there was no evidence of thrombosis. The isolation of *Enterobacter cloacae* from postmortem smears from the lungs and from heart blood cultures was attributed to postmortem contamination.

Histological examination

The lungs showed multiple foci of purulent-necrotizing pneumonia. Clusters of Gram-positive cocci were observed among the inflammatory cells in the alveoli (Fig. 3). A focal myocardial necrosis without evidence of bacteria or signs of myocardial infarction was found.

Cause of death

The cause of death was respiratory failure due to pneumonia following metastatic pyaemic abscesses secondary to *Staphylococcus aureus* septicaemia arising at the site of peripheral venous catheterization.

Case 3

Clinical course

A 56-year-old previously healthy man was hospitalized because of acute lumbago and sciatica. The diagnosis of herniation of the intervertebral disc between lumbar vertebra 4/5 was made by computerised tomography. The patient received conservative therapy and the pain was treated with several intramuscular injections of a

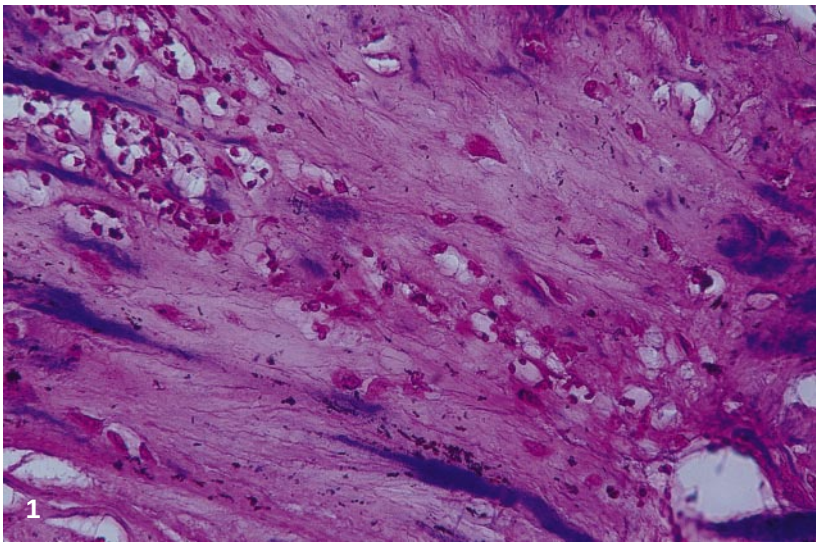

Fig. 1 Case 1 – Fibrinous vegetation of the aortic valve with Gram-positive cocci. No signs of underlying valvular disease (Gram staining, × 180)

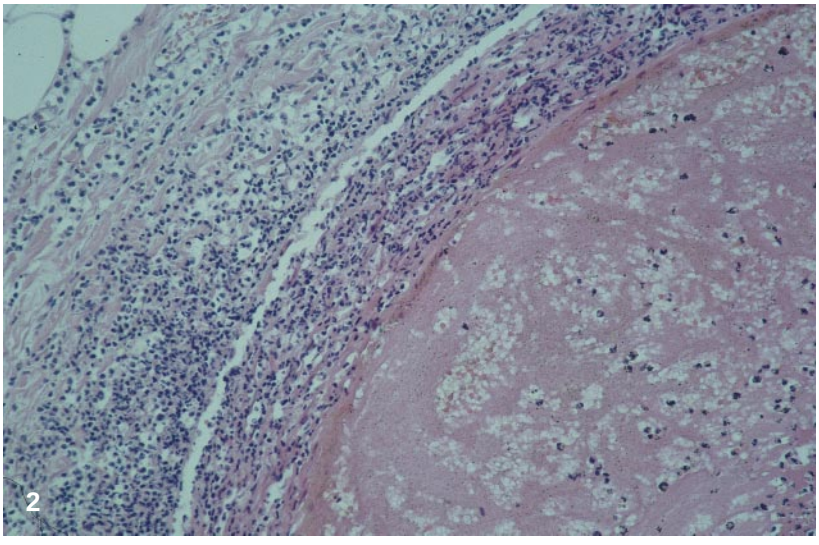

Fig. 2 Case 1 – Anterior descending branch of the left coronary artery: embolism of vegetations from the aortic valve. Polymorphonuclear infiltration of all coats of the vessel wall (hematoxilin-eosin, × 150)

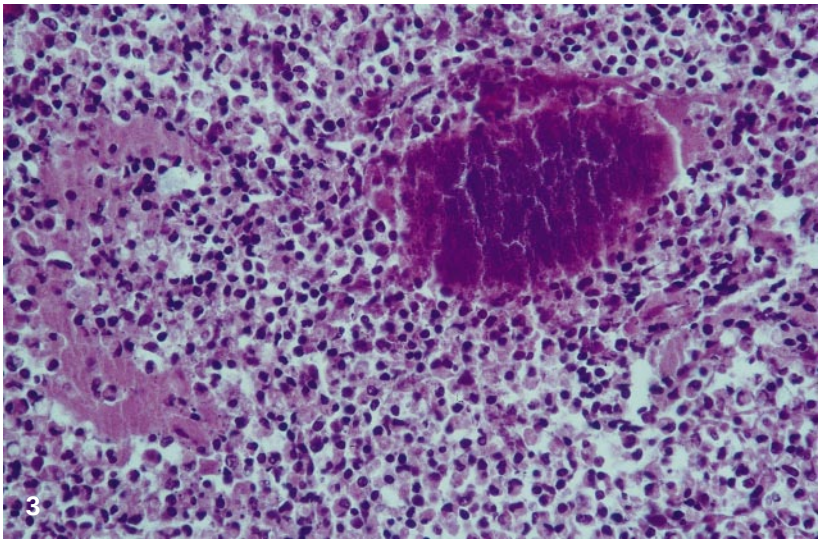

Fig. 3 Case 2 – Cluster of cocci with fibrin aggregations among the granulocytic infiltrate in the alveoli (hematoxilin-eosin, × 300)

nonsteroidal antirheumatic (diclofenac) to the gluteal regions on both sides for the next 21 days. On hospital day 22 the body temperature increased to 41.0 °C. Blood cultures were performed and antibiotic therapy with vancomycin was started empirically. Blood cultures identified *Staphylococcus aureus* on day 23 and the antimicrobial regimen was adjusted (flucloxacillin, gentamicin). Nuclear magnetic resonance tomography revealed various abscesses in both gluteal regions. During the next 24 h, the patient developed

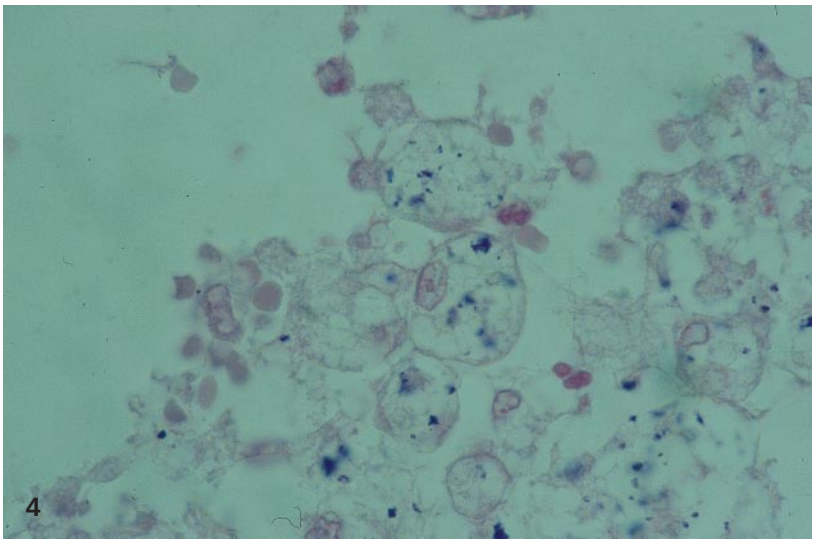

Fig. 4 Case 3 – Foam cells with Gram-positive cytoplasmatic inclusions within the gluteal abscesses (gram, × 960)

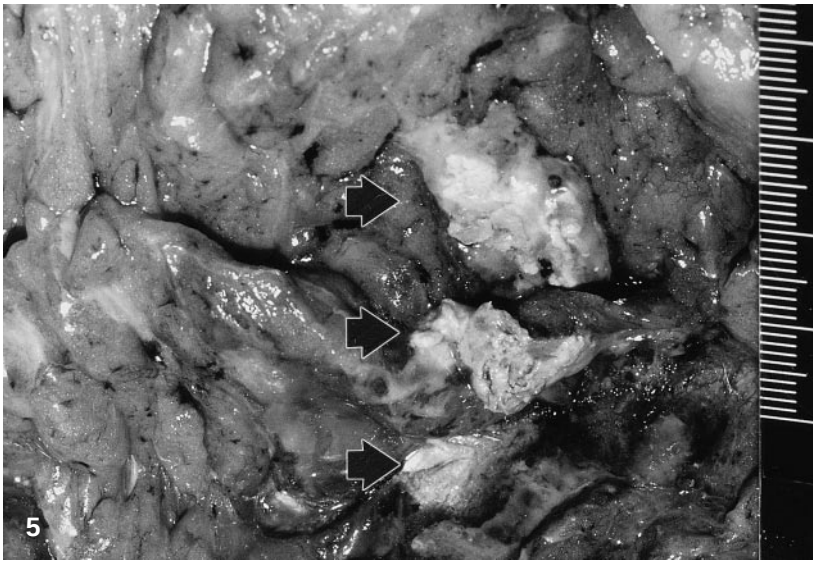

Fig. 5 Case 3 – Sharply demarcated gluteal abscesses (➚) with perifocal oedema of the surrounding gluteal fatty tissue

respiratory insufficiency with hypoxemia, acute renal failure and rapidly progressive somnolence. In spite of intensive support with endotracheal intubation, mechanical ventilation and hemodialysis, he died on day 25, within 3 days after the onset of signs of septicaemia.

Autopsy findings

A total of five purulent-necrotizing, sharply demarcated abscesses up to 4.5 cm in diameter and containing large amounts of pus, were found in the upper lateral quadrants of the gluteal tissue on both sides (Fig. 4). The gluteal fatty tissue and the gluteal muscles were oedematous. Furthermore an acute splenitis and generalised shock-associated changes in internal organs were obvious. *Staphyloccocus aureus* was isolated from smears taken after death from the gluteal abscesses. The growth of *Escherichia coli* and *Enterobacter cloacae* from postmortem heart blood cultures and culture specimens taken from the spleen was attributed to contamination.

Histological examination

Histologically, the gluteal abscesses showed an intralipomatous inflammation and liquefactive necrosis of fatty tissue, but no involvement of the gluteal musculature. A mass of necrotic white cells, foci of calcification and foam cells with Gram-positive cytoplasmatic inclusions were found (Fig. 5). There was a membranous encapsulation of the abscess formations by granulation tissue with neo-vascularization.

Cause of death

Death was attributed to septic shock with multi-organ failure due to *Staphylococcus aureus* septicaemia following intramuscular injections to both gluteal regions.

Discussion

Infection related to invasive iatrogenic injection procedures is extremely rare [7]. Septicaemia resulting from an intravenous catheterization runs a mild course and the incidence is presumed to be less than 1% even in high-risk patient populations [3, 15, 25]. *Staphylococcus aureus* septicaemia as a sequel to injections is predominantly a

complication found in intravenous drug abusers [4, 12, 28], in patients with progressive and disseminated malignancy [5] or in patients requiring long-term intravascular access [20, 25]. The immunocompromisation brought about by the severity of the underlying illness is presumed to be a major determinant of mortality [5, 30]. Therefore it has to be emphasized that the fatalities presented here originated from iatrogenic injection therapy for the treatment of non-severe and non-life-threatening underlying diseases. None of the patients suffered from any kind of metabolic disorder or immunodeficiency nor had received cortico-steroids or anti-mitotic agents. The patients were hospitalized throughout the entire period.

A variety of clinical studies and case reports of patients not known to be suffering from any severe underlying debilitating illness or immunological deficiency have reported the development of *Staphylococcus aureus* septicaemia due to diagnostic intervention or therapeutic approaches [1, 2, 8, 9, 13, 21, 26, 34]. Given the abundance of injections administered in clinical practice, fatal outcomes of such interventions are extremely rare. In a clinical series of 100 patients with septic phlebitis following the insertion of intravascular devices, no deaths could be attributed to septicaemia [2], although the authors do not mention whether autopsies were performed on all these deaths. Likewise, in other comprehensive clinical studies where death was attributed more frequently to the underlying illness, rather than to iatrogenic septicaemia [1, 21, 22], autopsies were not performed regularly, making it difficult to estimate mortality rates. It is reasonable to consider that fatalities due to nosocomial bloodstream infections are underdiagnosed and underreported, a fact ascribable to the major difficulty of physicians to differentiate whether the death of a patient can be attributed to the underlying disease process itself or is due to a nosocomial infection – when an autopsy is not performed. Therefore it is demanded that all doubtful cases of nosocomial bloodstream infections with fatal outcome should undergo a full medicolegal investigation. This investigation should not only deal with specific questions of proper medical care in individual cases, in general it should also focus on aspects of hospital hygienics and serve as a quality control to achieve appropriate preventive practices to minimize the incidence and mortality of nosocomial infections.

In cases of septicaemia due to indwelling catheters, the host, the micro-organism and the catheter material itself each play an interactive role in the pathogenesis of the infection [27]. Although the catheter tip itself may be what transfers the bacteria into the bloodstream, the skin entry site of the catheter or injection needle can also be the major portal of entry for the micro-organisms [17] with eventual access to the bloodstream through extraluminal migration along the catheter's tract [7, 27]. The skin can initially be colonized with *Staphylococcus aureus* or contamination can be derived from the hands of hospital personnel and other objects [33]. Once established in a hospital, micro-organisms are difficult to eradicate due to multiple antibiotic-resistance and interhospital transmission between patients and personnel. Another possibility is the direct contamination of the intravenous fluids or of the drugs used for intramuscular injections [27], but irrespective of the origin of the micro-organisms, such a mode of infection has to be classified as nosocomial.

In the presented cases, autopsies were performed within 2–4 days postmortem. This delay renders aetiopathogenetic conclusions more difficult. No focus for the staphylococcal infection other than the insertion site of the peripheral venous catheters or the intramuscular injections could be identified. Based on the clinical course, blood culture results, outcome of autopsy and histological findings, death was attributed directly to the staphylococcal infection following iatrogenic injection therapy.

In case 1, the patient showed typical signs of phlebitis [2] at the site of an indwelling peripheral venous catheter in the basilar vein, but no peripheral vein thrombosis was found at autopsy. The histological appearance of the coronary embolism and the myocardial infarction corresponded to a survival time of approximately 24–72 h following the embolism. Embolic coronary phenomena can be found in cases of infective endocarditis in 45–65% of autopsies [33]. In case 2, the fulminant course was attributed to pneumonia of *Staphylococcus aureus* type. Lungs are common sites of pyaemic abscess formation of *Staphylococcus aureus* septicaemia [31]. In case 3, only the fatty tissue of the gluteal region was involved in the inflammatory process without visual or histological signs of inflammation of the gluteal musculature, apart from oedema. Injections into the gluteal region are intended to be intramuscular but they are often actually administered into fatty tissue of the gluteal fat area [6]. The histological finding of foam cells with cytoplasmatic inclusions of small clusters of Gram-positive cocci tends to confirm the origin of septicaemia from adipose tissues.

Septicaemia rarely complicates intramuscular injections because the skin is only breached briefly and major vessels are not normally damaged. Only a few previously reported cases of fatal *Staphylococcus aureus* septicaemia followed intramuscular injection therapy [16, 26, 32, 35].

Some authors have defined intravenous catheter-related septicaemia as the finding of a positive blood culture in the absence of a focus of infection other than the catheter itself [14, 25]. Others point out that catheter-related septicaemia can only be determined by the identification of an identical organism in a culture of the catheter segment and in a peripheral blood culture [7, 18, 19].

From the forensic point of view, the diagnosis of fatal *Staphylococcus aureus* septicaemia following iatrogenic injections can only be confirmed unequivocally by postmortem examination. In most cases examined routinely, postmortem blood cultures will be unhelpful as they are contaminated due to putrefaction processes. However, smears taken at autopsy from a circumscribed focus as the potential source of infection, e.g. abscesses or soft tissue abscesses, can be of considerable value. In suspected cases, the clinical course and the results of intravital and postmortem blood cultures have to be evaluated critically.

To optimize aetiopathogenetic conclusions concerning the causal relationship between iatrogenic injections and

septic complications, the forensic investigation should ensure an immediate autopsy or at least postmortem blood sampling under sterile conditions. Parallel sampling of smears from skin and nasopharynx can be useful to identify the resident and transient bacterial flora of the deceased. To identify the source of origin of an infection, the investigation should also include sampling of smears from nasopharynx and throat of the medical personnel as potential carriers of micro-organisms. Postmortem specimens should include the injection site and uninjured skin (as control), lymphatic tissue (regional lymph nodes, spleen) and septic foci in parenchymatous organs. Phagotyping, identification of bacterial toxins, molecular biological characterization and immunohistochemical investigations [11, 23, 24, 29] of the appropriate specimens obtained postmortem in cases of very early forensic involvement could be efforts of potential evidential value regarding the aetiological proof.

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